CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Trifluridine-Tipiracil (Lonsurf) for metastatic Colorectal Cancer

July 6, 2018

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer conducted by the Gastrointestional Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer, a summary of submitted Provincial Advisory Group Input on trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer, and a summary of submitted Registered Clinician Input on trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of trifluridine-tipiracil (Lonsurf) for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

Health Canada issued a Notice of Compliance (NOC) for trifluridine-tipiracil (Lonsurf) for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents. The funding request under review by pCODR aligns with the patients described in the Health Canada indication.

Trifluridine-tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil (as tipiracil hydrochloride). The recommended dose of trifluridine-tipiracil (tablets) is a starting dose of 35 mg/m^2/dose administered orally with water, twice daily, within 1 hour after completion of morning and evening meals, on days 1 to 5 and days 8 to 12 of each 28-day cycle. The treatment cycle is repeated every 4 weeks as long as benefit is observed or until unacceptability toxicity occurs.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Three randomized control trials (RCTs) were included in this review[1,2,6]. Key efficacy and safety outcomes for all trials are summarized in Table 1. All were double-blind, parallel-group, two-armed, and placebo-controlled trials. RECOURSE and TERRA were phase III trials and J003-10040030 was a phase II trial. All investigated the efficacy and safety of trifluridine-tipiracil in patients that were

intolerant to or had failed standard therapies. Study medication was administered orally twice daily in 35mg/m^2/dose for days 1-5 and 8-12 in a 28 day treatment cycle. Patients also received best supportive care. Patients were randomized in a 2:1 ratio in all studies to receive trifluridine-tipiracil or placebo.

RECOURSE included patients from 13 countries, the majority were white (58%). Overall, 534 patients were assigned to the trifluridine-tipiracil group and 266 to the placebo group. TERRA included patients from three countries, all patients were Asian. Overall, 271 patients were assigned to the trifluridine-tipiracil group and 135 to the placebo group. J003-10040030 included patients from Japan, and all patients were Japanese. Overall, 114 patients were assigned to the trifluridine-tipiracil group and 58 to the placebo group.

Patient characteristics were balanced between treatment groups in all trials. Median age of patients ranged from 56-63 years with a male population ranging from 49-63%. Eastern Cooperative Oncology performance status (ECOG PS) of participants in RECOURSE was limited to 0-1 with approximately half with each status. In TERRA the same criterion applied however approximately ¾ of patients had an ECOG PS of 1. In J003-10040030 patients with an ECOG status of 2 were also included, however patients with ECOG PS 2 only made up 2.4% of the patient population; the majority (63%) had an ECOG status of 0.

Efficacy and safety outcomes are summarized in section 6.2.8.2 and Tables 9, 10 and 11.

Overall survival (OS) was the primary endpoint of all trials, defined as the time between randomization and death due to any cause. All trials reported statistically significant improvements in OS in favour of trifluridine-tipiracil treatment.

In RECOURSE formal OS analysis occurred once 571 deaths were observed. The median OS was 7.1 months in the trifluridine-tipiracil group and 5.3 in the placebo group. An absolute improvement in median OS of 1.8 months for treatment was reported (HR=0.68, 95%CI: 0.58-0.81, p<0.001). The median follow-up time for OS analysis was 11.8 months. The intent to treat (ITT) population was used for this analysis (n=800).

Updated survival analysis for RECOURSE was reported in a conference abstract. Updated survival data were collected on October 8th, 2014[9]. This was 7.4 months following the original cut-off date of January 24th, 2014 stipulated in the RECOURSE protocol. Median OS was 7.2 months in the trifluridine-tipiracil group and 5.2 months in the placebo group. A slightly higher absolute improvement in median OS of 2.0 months in favour of the treatment group was reported (HR=0.69, 95%CI: 0.59-0.81, p<0.0001). Median follow-up time for the updated analysis was 19.1 months[10]. The ITT population was used for this analysis (n=800).

In TERRA, formal OS analysis occurred once 288 deaths were observed. The median OS was 7.8 months in the trifluridine-tipiracil group and 7.1 months in the placebo group. An absolute improvement in median OS of 0.7 months for treatment was reported (HR=0.79, 95%CI: 0.62-0.99, p=0.035). Median follow-up time for OS analysis was 13.8 months and 13.4 months for the trifluridine-tipiracil and the placebo group respectively. The ITT population was used for this analysis (n=406).

In J003-10040030 OS analysis occurred once 121 deaths were observed. The median OS was 9.0 months in the trifluridine-tipiracil group and 6.6 months in the placebo group. An absolute improvement in median OS of 2.4 months for treatment was reported (HR=0.56, 95%CI: 0.39-0.81, p=0.0011). Median follow-up time for OS analysis was 11.3 months. The efficacy population was used in this analysis (n=169).

All trials reported statistically significant improvements in progression free survival (PFS) in favour of trifluridine-tipiracil treatment.

The median PFS in RECOURSE was 2.0 months for the trifluridine-tipiracil group compared to 1.7 months in the placebo group (HR=0.48, 95%CI: 0.41-0.57, p<0.001). In TERRA the median PFS was 2.0 months and 1.8 months for the trifluridine-tipiracil and placebo groups respectively (HR=0.43, 95%CI: 0.34-0.54, p<0.001). In J003-10040030 the median PFS was 2.0 and 1.0 months for the trifluridine-tipiracil and placebo groups respectively (HR=0.41, 95%CI: 0.28-0.59, p<0.0001).

Direct measures of health related quality of life (QoL) were not reported in any of the included studies.

All three trials provided data on harm outcomes using an as-treated population (AT). All trials indicated that certain adverse events had higher incidence rates in the trifluridine-tipiracil group compared to placebo (e.g. neutropenia, anemia, and leukopenia). Serious adverse events (SAEs) are AEs that led to death, were life threatening, led to admission or extension of hospital stay, and/or turned into or triggered lasting disabilities or dysfunctions. RECOURSE and J003-10040030 report febrile neutropenia as their SAE of greatest incidence. Incidence of SAEs was similar between treatment groups for RECOURSE and TERRA, but was higher for J003-10040030 patients in the trifluridine-tipiracil group compared to placebo.

Withdrawal due to adverse events was similar between treatment groups for all trials. In RECOURSE 10.3% of patients in the trifluridine-tipiracil and 13.6% of patients in the placebo withdrew due to adverse events. In TERRA 10% and 9.6% of patients withdrew from the treatment and placebo groups and in J003-10040030 4% and 2% of patients withdrew from either group due to adverse events. In the RECOURSE trial, grade three or greater adverse events occurred in 69% of patients in the treatment arm and 52% of the patient in the placebo arm. Incidence of SAEs was at 29.6% in the trifluridine-tipiracil group and 33.6% in the placebo group. In the TERRA trial, 45.8% in the treatment arm experienced an adverse event and 10.4% in the placebo arm. Incidence of drug related SAEs was at 23.2% and 23% in the trifluridine-tipiracil and placebo groups respectively.

In the J003-10040030 grade three or greater adverse events occurred in 69% of patients in the treatment arm and 16% of patients in the placebo arm. SAEs occurred in 19% of the patients treated with trifluridine-tipiracil and 9% of patients in the placebo group.

In all trials the main adverse events that differed between treatment groups (>10% difference) were neutropenia, leukopenia, and anemia. Vomiting also had a greater than 10% difference between groups in the J003-10040030 trial. One treatment-related death occurred in RECOURSE due to septic shock and no treatment-related deaths occurred in J003-10040030 or TERRA.

Table 1: Highlights of Key Outcomes

	RECOURSE[1]		TERRA [2]		J003-10040030[6]	
	Trifluridine-tipiracil (n=534)	Placebo (n=266)	Trifluridine-tipiracil (n=271)	Placebo (n=135)	Trifluridine-tipiracil (n=112)	Placebo (n=57)
Median OS in months (95%CI)	7.1 (6.5-7.8)	5.3 (4.6-6.0)	7.8 (7.1-8.8)	7.1 (5.9-8.2)	9.0 (7.3-11.3)	6.6 (4.9-8.0)

	RECOURSE[1]		TERRA [2]		J003-10040030[6]	
	Trifluridine-tipiracil (n=534)	Placebo (n=266)	Trifluridine-tipiracil (n=271)	Placebo (n=135)	Trifluridine-tipiracil (n=112)	Placebo (n=57)
HR (95%CI)	0.68 (0.58-0.81)		0.79 (0.62-0.99)		0.56 (0.39-0.81)	
p-value	<0.001		0.035		0.0011	
Median PFS in months (95%CI)	2.0 (1.9-2.1)	1.7 (1.7-1.8)	2.0 (1.9-2.8)	1.8 (1.7-1.8)	2.0 (1.9-2.8)	1.0 (1.0-1.0)
HR (95%CI)	0.48 (0.41-0.57)		0.43 (0.34-0.54)		0.41 (0.28-0.59)	
p-value	<0.001		<0.001		<0.0001	
Harms Outcome, n (%)	Trifluridine-tipiracil (n=533)	Placebo (n=265)	Trifluridine-tipiracil (n=271)	Placebo (n=135)	Trifluridine-tipiracil (n=113)	Placebo (n=57)
AE Grade ≥3	370(69)	137(52)	124(46)	14(10)	78(69)	9(16)
AE (any grade)	524(98)	247(93)	244(90)	70(52)	111(98)	52(91)
WDAE	21(4)	5(2)	27(10)	13(9.6)	5(5)	1(2)
[Abbreviations] AE = adverse event, CI = confidence interval, HR = hazard ratio, OS = overall survival, PFS = progression free survival, WDAE = withdrawal due to adverse event						

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, there are a number of symptoms associated with mCRC that impact quality of life, which include fatigue, bloody stools, diarrhea or constipation, anemia, abdominal cramping, and bowel obstruction. Almost all CCC survey respondents (93%) reported they experienced symptoms from their CRC. Pain, diarrhea and fatigue resulting from the cancer were reported to be the most important and difficult to control symptoms. Most patients feel their CRC-induced symptoms interfere with their quality of life and their daily activities, citing they are not able to function "normally" in their family or work settings. Stomas and pain were identified as limitations exerting psychological impacts resulting from CRC; and respondents also noted experience with anxiety, depression and sleep problems. CCC noted CRC also significantly impacted the lives of caregivers who are fraught with enormous financial, physical and psychological challenges when caring for their loved ones. According to the survey and telephone interview results, the majority of patients accessed current combination chemotherapies such as FOLFOX, FOLFIRI and/or capecitabine with bevacizumab; other therapies, such as cetuximab, panitumumab, regorafenib, and pembrolizumab, were accessed much less frequently. Approximately half of respondents reported current therapies were effective at controlling their cancer-induced symptoms. Most patients cited fatigue, nausea, diarrhea, hair loss, vomiting, mouth sores, and hand and foot syndrome as being the most common side effects from these CRC treatments, with chemo-induced fatigue, nausea, and diarrhea identified as the most difficult to tolerate. Approximately half of survey respondents replied "yes" when asked if some of their needs were not being met by the current drugs available to treat their CRC. CCC indicated that for patients with refractory mCRC, limited therapeutic options exist to treat their disease, regardless of RAS mutational status; and the survey results clearly highlight patients' desire to be permitted access to therapies that will effectively control their disease with respect to overall survival, progression-free survival, and, in particular, improve quality of life. The 20 survey and interview respondents who had direct experience with trifluridine-tipiracil

received the drug in multiple lines of therapy (first to sixth-line of treatment) and survey respondents indicated accessing the drug either through a clinical trial, insurance plan, or self-pay. Patients cited manageable side effects with trifluridine-tipiracil that included fatigue, diarrhea, constipation, low blood counts, and abdominal discomfort, of which fatigue was considered the most difficult to tolerate. When asked to compare the side effects they experienced with trifluridine-tipiracil to other therapies they have taken, surveyed patient respondents reported milder/less side effects overall with trifluridine-tipiracil but noted issues with blood counts and fatigue. Interviewed respondents also noted better tolerance of trifluridine-tipiracil compared to other therapies. There were no survey respondents who rated their quality of life as low/severely impacted by trifluridine-tipiracil; all patients rated a 7 or greater on the 10-point scale (where 10 equates with high/normal living), demonstrating patients were able to achieve a high quality of life while on the therapy. Similar quality of life ratings were reported by the interview respondents.

Provincial Advisory Group (PAG) Input

Input was obtained from seven provinces (Ministries of Health and/or cancer agencies) and federal drug program participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- The value of trifluridine-tipiracil given the very modest overall survival, short progression-free survival, low objective response rates and occurrence of serious adverse events

Economic factors:

- Cost of supportive therapy (e.g. anti-emetics, granulocyte colony-stimulating factor)
- Resources required to monitor and treat serious adverse events

Registered Clinician Input

The clinicians providing input identified that although regorafenib is approved for metastatic colorectal cancer after previous chemotherapy, regorafenib is not funded in any province. They indicated that trifluridine-tipiracil (TAS-102) provides a treatment option that appears to be better tolerated than regorafenib. They noted that the number of patients who would be eligible to receive would be small relative to the incident population. Please see below for details from the clinician inputs.

Summary of Supplemental Questions

Critical appraisal of the findings of a systematic review and network meta-analysis comparing the efficacy and safety of trifluridine-tipiracil to regorafenib can be found in Section 7. Of note, regorafenib is not currently publically funded in any province.

The pCODR methods team completed a critical appraisal of the findings from a systematic review and network meta-analysis comparing treatment efficacy and safety between trifluridine-tipiracil and regorafenib. The results of the comparison indicated that treatment with either drug resulted in similar OS, PFS, ORR, and DCR outcomes. Safety outcomes were the main difference between treatment options. Overall, regorafenib had greater all-grade and grade 3-5 AE incidence. Subgroup analyses indicated a difference in toxicity profile between treatments. The results were presented as potentially informative

to clinical practice given individual patient histories. Treatment sequence and superiority were not determined.

The conclusions of the study are limited by some heterogeneity between the compared studies in patient characteristics and the fact that it is an indirect as opposed to direct comparison between drugs.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for trifluridine-tipiracil for the treatment of adult patients with mCRC

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Performance Status	RECOURSE and TERRA limited ECOG status to ≤1. The majority of patients in RECOURSE had an ECOG status of 0 (56.0%). The majority of patients in TERRA had an ECOG status of 1 (76.8%). J003 included patients with ECOG status of 2, however they made up a very small portion of enrolled patients (n=5, 2%). The majority of patients had an ECOG status of 0 (63.3%).	Do the trial results apply to patients with an ECOG PS of 2 or greater? If so, why?	Interpretation of the trial results is mostly limited to patients with an ECOG status of 1 or 0.
	Metastatic Sites	RECOURSE and J003-10040030 reported the exclusion criteria of serious comorbidities. RECOURSE, TERRA, and J003-10040030 excluded patients with known brain or leptomeningeal metastases under this criteria. All trials required patients to have metastatic lesion(s) to enroll.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population?	No the exclusion of these patients does not limit the interpretation of the trial results with respect to the target population, it is very uncommon to have these sites of metastatic disease.
	Ethnicity or Demographics	RECOURSE included 101 centres from 13 countries and the majority of patients were white (57.6%). TERRA included 30 centres from 3 countries and all patients were Asian. J003 included multiple centres from Japan and patient race was not reported.	Is this representative of how patients present in Canadian practice?	Yes, the trials were from a wide selection of ethnicity given the enrollment from multiple countries and were fairly representative of patients seen in Canada.
	Disease site	The patient population in all three studies were previously treated mCRC patients.	Do trial results apply to patients with small bowel cancer?	There is limited evidence on treatment of small bowel, based on clinical consensus small bowel cancer is treated similar to colorectal cancer, but at the discretion of treating oncologist. Of note, small bowel cancer is extremely rare.
	Line of therapy	All trials required patients to have received at least 2 standard chemotherapy regimens for mCRC and be refractory or intolerant to them.	Do the trial results apply to patients who have had only one or two lines of standard chemotherapy regimens? If so, why?	Results are generalizable to KRAS mutant patients with contraindications to bevacizumab and patients with DPD deficiency, there is a small number of these patients who have few treatment options and who would benefit from earlier treatment with trifluridine-tipiracil.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Comparator	Standard of Care	The comparator for all trials was placebo plus BSC.	Health Canada approved regorafenib in 2013 for treatment in mCRC patients that are at third or later line of therapy. Clinical trial participation and BSC are also treatment options. If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	BSC is an appropriate comparator. Regorafenib is not funded publically in any province and remains only available through private insurance. When the trials for trifluridine-tipiracil were completed, BSC was the comparator.
Setting	Countries participating in the Trial	RECOURSE was conducted in 13 countries, TERRA in 3, and J003 in Japan. None of the trials included centres in Canada.	Do trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries participating in the trials and Canada?	There are differences in practice patterns between countries, however, management of patients on the trial protocols were not dissimilar to Canadian practice.

Abbreviations: AE - adverse event; BSC - best supportive care; DPD - dihydropyrimidine dehydrogenase deficiency; ECOG - Easter Cooperative Group Performance ; KRAS - Kirsten Rate Sarcoma Oncogene; mCRC - metastatic colorectal cancer

1.2.4 Interpretation

Need and Burden of Disease

Colorectal cancer represents the second and third most common causes of cancer death in Canadian males and females, respectively. Specifically, the Canadian Cancer Society estimates that, in 2017, 26,800 Canadians were diagnosed with, and 9,400 Canadians died as a consequence of, colorectal cancer.[25,26]

If a patient develops colorectal cancer with metastases not amenable to surgical resection, the disease is incurable and a palliative approach is most appropriate. To provide a recommendation about therapy that controls the disease, maintains or improves quality of life, and delays death, Medical Oncologists consider the quality of the available evidence, as well as the patient's preference and factors such as performance status, relevant comorbidities, and primary tumor location. Typically, treatments use a fluoropyrimidine (e.g.: 5-Fluorouracil, Capecitabine), Irinotecan, and/or Oxaliplatin in combination or in sequence with an anti-VEGF therapy (e.g.: Bevacizumab) or, if *RAS* wild-type is confirmed, an anti-EGFR therapy (e.g.: Cetuximab, Panitumumab).

Recognizing that; 1) initial use of Trifluridine-Tipiracil would be limited to patients with metastatic colorectal cancer that has been previously been treated with at least fluoropyrimidine, Oxaliplatin, and Irinotecan (as in the seminal trials) and 2) that there is attrition from one systemic line to the next due to various considerations (personal preference, relevant comorbidity, and/or a decline in performance status), the Clinical Guidance Panel (CGP) estimates that likely up to 20% of the 9,400 Canadians who die with colorectal cancer would truly be potential candidates for treatment with Trifluridine-Tipiracil. Untreated, historical series describe survivals in mCRC in the range of six to ten months.[28,29] However, trifluridine-tipiracil is indicated at the end of a series of established treatments and compared against placebo which mimics best supportive care and no active treatment.

Effectiveness & Safety

Two randomized, double-blind, placebo-controlled, phase III clinical trials (*RECOURSE* and *TERRA*) have established that, in patients with metastatic colorectal cancer (previously treated with fluoropyrimidine, Oxaliplatin, and Irinotecan), the combination of Trifluridine (a thymidine analogue) and Tipiracil (known as TAS-102 -an inhibitor of thymidine phosphorylase that modifies Trifluridine clearance) offers a statistically significant and clinically meaningful prolongation of overall survival when compared with placebo. Indeed, there is a clear separation of the Kaplan-Meier survival curves and the hazard ratios were 0.68 and 0.79, respectively. This benefit persists irrespective of whether patients have received prior treatment with anti-VEGF therapy (e.g.: Bevacizumab), anti-EGFR therapy (e.g.: Cetuximab, Panitumumab), and/or a multi-targeted tyrosine kinase inhibitor (e.g.: Regorafenib).

Patient advocacy groups indicate that patients want access to therapies that maintain quality of life, delay progression, and prolong survival. They accept that active treatment introduces the risk of toxicity. However, the frequency of grade ≥ 3 toxicities attributed to Trifluridine-Tipiracil is low and even despite the adverse effects experienced (e.g.: anemia, thrombocytopenia, neutropenia, risk of febrile neutropenia, fatigue), treatment still delays the time to a decline in performance status to ECOG ≥ 2 and is considered manageable.

The oral route of administration of trifluridine-tipiracil minimizes the time patients need to devote to their treatment and does not burden the cancer facilities' outpatient/daycare units.

Following the posting of the pERC Initial Recommendation, the CGP noted a number of concerns raised by pERC of trifluridine-tipiracil for mCRC. To address these questions and concerns, the CGP provided the comments below.

- Two trials independently established a statistically significant and more importantly a clinically meaningful overall survival and progression-free survival advantage. To focus solely on the absolute difference, to the exclusion of the hazard ratios and Kaplan-Meier curves is a disservice to the evidence. The RECOURSE and TERRA trials establish a relevant 32% and 21% advantage in overall survival and a 52% and 57% advantage in progression-free survival, respectively. This benefit is reflected in the clear separation of the curves when compared to the relevant comparator of placebo (best supportive care alone).
- Trifluridine-Tipiracil toxicities are generally speaking easily managed by any medical oncologist.
- While the CGP agree that quality of life was not established using a conventional and validated tool, a 34% delay in a patient's decline from performance status ECOG 0 or 1 to 2 or greater is a clinically significant benefit to the patient.
- There is no publically available option in Canada for patients who have exhausted the currently established standard of care (e.g.: fluoropyrimidine, Irinotecan, Oxaliplatin). As such, Trifluridine-Tipiracil would provide an option for patients who,
    - by virtue of their comorbidities, lose the option of Bevacizumab;
    - by virtue of their tumor's molecular profile (e.g.: RAS mutation) or the proximal location of their primary, lose the option of anti-EGFR therapy (e.g.: Panitumumab, Cetuximab);
    - by virtue of another molecular marker (e.g.: BRAF mutation), have a predefined poorer response to treatment and prognosis; or
    - by virtue of their inherent deficiency in dihydropyrimidine dehydrogenase, are not able to receive a fluoropyrimidine (the basic building block of most treatments for metastatic colorectal cancer) because it becomes unjustifiably toxic.[50]
- The CGP reiterated that NICE in the United Kingdom recommended that Trifluridine-Tipiracil be used "within its marketing authorization" given its favorable pharmacoeconomics.[79]
- They also reiterated that Trifluridine-Tipiracil has been deemed "more clinically cost-effective than Regorafenib".[51,52]

1.3 Conclusions

Trifluridine-Tipiracil provides an additional line of therapy for patients who have exhausted the treatments made publically available and/or for those patients who, for various reasons (e.g., relevant medical comorbidity, proximal primary tumor site, etc.), were not considered appropriate for treatment with anti-VEGF therapy (e.g., bevacizumab), anti-EGFR therapy (e.g., cetuximab, panitumumab), and/or multi-targeted tyrosine kinase inhibitor (e.g., regorafenib) in their prior lines of therapy.

The strength of the evidence in this setting is compounded by the complementary nature of the two phase 3 clinical trials; with both studies demonstrating statistical superiority in the important end-points. The evidence is also supported by a phase 2 trial (J003-10040030). Findings are generalizable to the Canadian population of patients with metastatic colorectal cancer and provide another effective treatment option for this all-too-common condition. Taken together, these published high-quality randomized controlled trials establish that Trifluridine-Tipiracil represents a tolerable treatment, there is a net overall clinical benefit

over best supportive care (as mimicked by placebo) and, as such, provides a valuable and novel addition to the armamentarium medical oncologists use to help patients combat their metastatic colorectal cancer.

This impression is congruent with those established by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

In making this conclusion, the Clinical Guidance Panel also considered that:

- Patients should not be offered Trifluridine-Tipiracil if they have a poor performance status (ECOG 2, 3, or 4) or significant impairment of their bone marrow, hepatic, or renal function.
- Patients should not be withdrawn from their current regimen to be switched to Trifluridine-Tipiracil until they have either progressed on, or demonstrated intolerance to, the current regimen.
- Regorafenib is not listed on the publically funded in any provinces; therefore, it can only be accessed by patients with private insurance or the means to cover the drug's cost. The sequencing of Trifluridine-Tipiracil and Regorafenib will remain a discussion between the patient and their Medical Oncologist. Nonetheless, best supportive care (as mimicked by placebo) remains the appropriate relevant comparator for Trifluridine-Tipiracil in the Canadian context.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

The separation of a cell into two daughter cells depends upon replication of the original DNA template. However, failure of a cell to overcome an impairment in DNA synthesis triggers apoptosis. Disruption of DNA replication by incorporation of chain-terminating nucleoside analogues into DNA and/or depletion of the native purine (adenosine and guanosine) and pyrimidine (cytidine and thymidine) deoxynucleosides essential to this process have been two successful cancer therapy strategies.

Trifluridine is an analogue of thymidine. It differs from thymidine only by the presence of a trifluoromethyl group (-CF_3) in place of the methyl group (-CH_3). Like thymidine, it can be phosphorylated by thymidine kinase in preparation for incorporation into DNA. Incorporation of Trifluridine into DNA occurs to a significantly greater degree in tumor tissue than in normal tissues, thus preferentially targeting cancer cells. However, the trifluoromethyl group prevents extension of the DNA and, thereby, results in chain termination.[33,34] Further, phosphorylation of Trifluridine inhibits thymidylate synthase, the only enzyme to produce deoxythymidine monophosphate (dTMP), one of the essential precursors for DNA synthesis.

The value of Trifluridine alone as an anti-cancer agent is limited by its very rapid degradation by thymidine phosphorylase. However, when combined with Tipiracil, an inhibitor of thymidine phosphorylase, at a 1.0 : 0.5 molar ratio, more favorable pharmacokinetics and pharmacodynamics result. Twice daily oral dosing of this combination of Trifluridine-tipiracil favors incorporation into DNA and maximizes its anti-cancer activity.

Of note, thymidine phosphorylase is identical to platelet-derived endothelial cell growth factor (PD-ECGF), a molecule that encourages angiogenesis. Therefore, inhibition of thymidine phosphorylase by Tipiracil not only prevents the degradation of Trifluridine but may also undermine angiogenesis, one of the hallmarks of cancer.

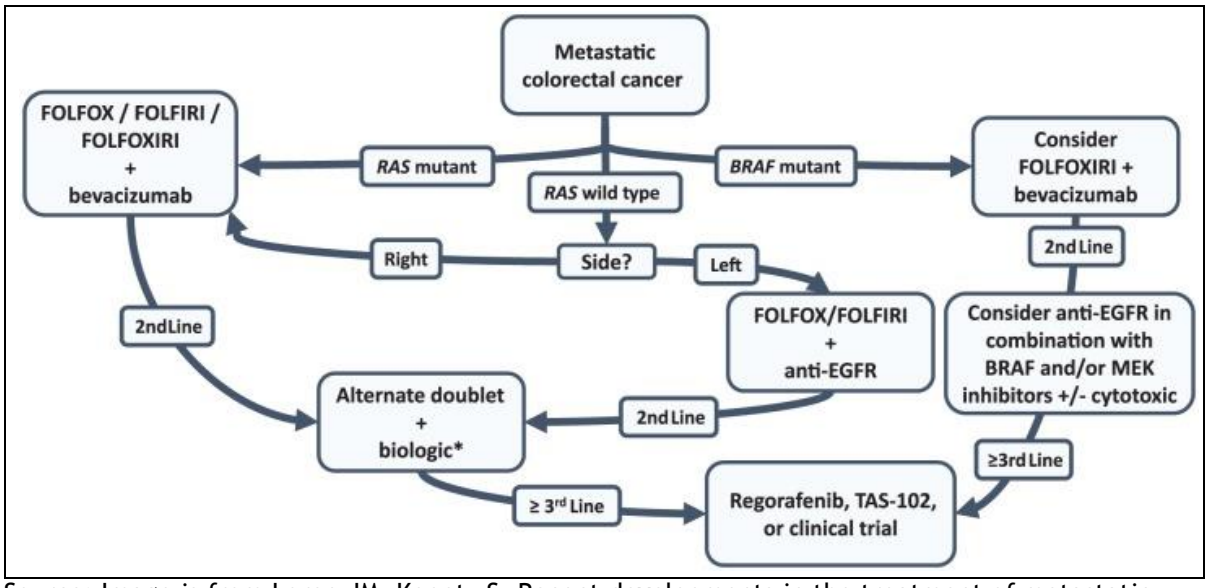
Trifluridine-Tipiracil (Lonsurf®) was approved by the US Food and Drug Administration in September 2015 and the European Medicines Agency in April 2016.

The Canadian Cancer Society estimates that, in 2017, 26,800 Canadians would be diagnosed with, and 9,400 Canadians would die as a consequence of, colorectal cancer. As such, colorectal cancer represents the second most common cause of cancer death in males and third most common cause of cancer death in females. [26] It is second only to lung cancer when potential years of life lost are considered.

2.2 Accepted Clinical Practice

Other than in very specific situations where resection of a liver or lung metastasis is possible, metastatic colorectal cancer is considered an incurable situation. Untreated, historical series describe survivals in the range of six to ten months.[28,29] Although the treatment of patients with metastatic colorectal cancer continues to evolve, it is now best thought of as a continuum of care where the evidence-based treatment options are administered, with consideration to biomarkers and primary tumor location, in combination or in sequence with the intent to carefully balance a patient's quality of life with their life prolonging effects.

This flow chart describes the potential treatment options for patients with colorectal cancer:[35]



Source: Image is from Loree JM, Kopetz S. Recent developments in the treatment of metastatic colorectal cancer. Ther Adv Med Oncol. 2017 Aug;9(8):551-64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5524248 Used under the creative commons licence (CC BY-NC 4.0) https://creativecommons.org/licenses/by-nc/4.0/

With chemotherapy,[36,37] targeted agents,[38] and a favorable cancer biology[39,40] (e.g.: absence of mutations in *RAS* or *BRAF*, distal primary tumor location), median survivals are now reliably measured in the thirty to thirty-six month range. Contemporary systemic therapies are cost effective,[41-45] delay the onset of tumor-related symptoms, and improve quality of life.[46,47] Despite these improvements, however, unfavorable factors (e.g.: mutations in *BRAF*, proximal primary tumor location) can still be associated with survivals under eighteen months.

Conventional chemotherapeutic agents	Monoclonal antibodies	Small molecule inhibitor
	Directed against the	of multiple membrane-bound and intracellular kinases involved in normal cellular function and pathologic processes
Fluoropyrimidines such as **5-Fluorouracil** (often modulated with Leucovorin) and **Capecitabine**	Vascular Endothelial Growth Factor (e.g.: **Bevacizumab**)	**Regorafenib**
Irinotecan	Vascular Endothelial Growth Factor Receptor (e.g.: **Aflibercept**, **Ramucirumab**)	
Oxaliplatin	Endothelial Growth Factor Receptor (e.g.: **Panitumumab**, **Cetuximab**) provided no mutation in *RAS* is detected and the primary tumor arises in the distal colon	

2.3 Evidence-Based Considerations for a Funding Population

TAS-102 (Trifluridine-Tipiracil) was best evaluated in the *RECOURSE* study, a prospective, multi-national, randomized, double-blind, parallel-arm clinical trial.[1] Between June 2012 and October 2013, sites in Japan, the United States, Europe, and Australia enrolled 1,002 patients with a good performance status (ECOG 0 or 1) and biopsy-proven colorectal cancer who had progressed on, or were intolerant to, at least two prior lines of the aforementioned systemic therapies. It then randomized 800 eligible patients in a 1:2 fashion to best supportive care plus either placebo or TAS-102 (Trifluridine-Tipiracil) at a dose of 35 mg/m^2 po BID. The pills were taken on days one

through five and eight through twelve in every twenty-eight day cycle. Up to three dose reductions (in decrements of 5 mg/m^2) were allowed. No cross-over was permitted. The treatment was continued until death, severe adverse event, clinical progression, or disease progression (as per RECIST 1.1 criteria). Radiologic assessments were performed every two cycles. The treatment arms were well balanced. Over 99% of patients received a fluoropyrimidine (e.g.: 5-Fluorouracil, Capecitabine), Irinotecan, Oxaliplatin, and Bevacizumab as part of their prior systemic anticancer therapy. Just over 50% of patients had received an anti-EGFR monoclonal antibody (e.g.: Panitumumab, Cetuximab). About 20% had received Regorafenib. Overall, about 60% had received six or more lines of therapy. 90% had disease that was refractory to a fluoropyrimidine. Approximately 42% of patients on both arms received additional systemic therapy following participation in this trial. The median dose intensity was 89% for the TAS-102 group and 94% for the placebo group.

The primary end-point of overall survival was achieved: Median overall survival was 7.1 months for TAS-102 and 5.3 months for placebo (HR 0.68, $CI_{95\%}$ 0.58-0.81, $p < 0.001$). The one-year overall survival rates were 27% and 18%, respectively. This benefit was observed in nearly all pre-specified subgroups. In the multivariate Cox regression analysis, time since diagnosis of first metastasis, performance status, and number of metastatic sites were prognostic. None of the stratification factors was predictive. The efficacy of TAS-102 remained even if 5-Fluorouracil was used as a component of the immediately preceding therapy (disease refractory to 5-Fluorouracil) and if the patient had received Regorafenib.

Source: Mayer RJ, Van CE, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14;372(20):1909-19.

Secondary end-points	**TAS-102** (*n* = 534)	**Placebo** (*n* = 266)	**Statistics**
Progression free survival	2.0 months	1.7 months	HR 0.48, $CI_{95\%}$ 0.41-0.57, $p < 0.001$
Objective response rate	1.6%	0.4%	$p = 0.29$
Disease control rate	44%	16%	$p < 0.001$
Median time to decline of performance status to ECOG ≥ 2	5.7 months	4.0 months	HR 0.66, $CI_{95\%}$ 0.56-0.78, $p < 0.001$

Source: Mayer RJ, Van CE, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14;372(20):1909-19.

Safety and Adverse Events	**TAS-102** (*n* = 533)		**Placebo** (*n* = 265)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any event	98%	69%	93%	52%
Any serious event	30%		34%	
Most common events				
Nausea	48%	2%	24%	1%
Emesis	28%	2%	14%	<1%
Anorexia	39%	4%	29%	5%
Fatigue	35%	4%	23%	6%
Diarrhea	32%	3%	12%	<1%
Abdominal pain	21%	2%	18%	4%
Fever	19%	1%	14%	<1%
Asthenia	18%	3%	11%	3%
Events associated with Fluoropyrimidine	4%	4%	0%	0%
Febrile neutropenia	8%	<1%	6%	0%
Stomatitis	2%	0%	2%	0%
Hand-foot syndrome	<1%	<1%	<1%	<1%

Safety and Adverse Events	**TAS-102** (*n* = 533)		**Placebo** (*n* = 265)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Cardiac ischemia				
Laboratory Abnormalities				
Neutropenia	67%	38%	<1%	0%
Leukopenia	77%	21%	5%	0%
Anemia	77%	18%	33%	3%
Thrombocytopenia	42%	5%	8%	<1%
Increased ALT	24%	2%	27%	4%
Increased AST	30%	4%	35%	6%
Increased bilirubin	36%	9%	26%	12%
Increased alkaline phosphatase	39%	8%	45%	11%
Increased creatinine	13%	<1%	12%	<1%

Post-marketing surveillance studies[48] have confirmed that, at least in Japan, the safety profile and adverse drug reactions were similar to the *RECOURSE* clinical trial. The first post-marketing surveillance study in Japan concluded, given the neutropenia, to emphasize careful monitoring for febrile neutropenia around day fifteen of the first cycle. The dosing considerations in the Health Canada product monograph for trifluridine-tipiracil noted that "Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor blood counts, but at a minimum, prior to each treatment cycle."

In Canada, there is regional variability in practice patterns. However, patients with metastatic colorectal cancer are often first treated with FOLFIRI or FOLFOX. Use and timing of a biologic/targeted therapy (e.g.: Bevacizumab, Panitumumab, Cetuximab) depends on the patient's comorbidities and preferences, a molecular analysis of the tumor for mutations in *RAS* and *BRAF*, and the site of the primary tumor (distal *versus* proximal). Regorafenib is not uniformly available on Cancer Drug Benefit Lists across Canada, but can still be accessed if patients are willing to pay for it.

Until evidence surfaces to support the efficacy and safety of Trifluridine-Tipiracil in earlier lines of therapy or in combination with other agents, any funding criteria in Canada would follow the eligibility criteria of the *RECOURSE* study. Therefore, it is anticipated that patients' access to Trifluridine-Tipiracil will remain limited (assuming that 70% of the 9,400 Canadians with metastatic colorectal cancer are eligible to pursue systemic therapy and recognizing the significant attrition from line to line of therapy,[49] the number of patients eligible to receive Trifluridine-Tipiracil would amount to less than 3,000 patients). However, because Trifluridine is not metabolized by dihydropyrimidine dehydrogenase, Trifluridine-Tipiracil is considered safe for use in patients with a deficiency in dihydropyrimidine dehydrogenase, a situation where the use of fluoropyrimidines such as 5-Fluorouracil and Capecitabine becomes unjustifiably toxic.[50]

In August 2016, the National Institute for Health and Care Excellence (NICE) in the United Kingdom recommended the use of Trifluridine-Tipiracil "within its marketing authorization." It has also been deemed "more clinically cost-effective than Regorafenib."[51,52] A retrospective comparison with Regorafenib in Japanese patients suggested that TAS-102 had "similar efficacy but … different toxicities."[53]

Research is underway to establish whether single nucleotide polymorphisms in the genes involved in Trifluridine metabolism and Tipiracil excretion (e.g.: *ENT1*, *MATE1*, *OCT2*) may serve as predictive and/or prognostic markers for patients treated with TAS-102.[54]

Despite evidence-based improvements in survival, there remains a "significant need for well tolerated [and] effective treatment options for patients with metastatic colorectal cancer who are refractory to standard [therapies]."[55]

2.4 Other Patient Populations in Whom the Drug May Be Used

While this CADTH evaluation focuses on the use of Trifluridine-Tipiracil in refractory metastatic colorectal cancer, clinical trials are underway to evaluate whether it can be used in earlier lines of therapy and/or in combination with other agents.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Colorectal Cancer Canada (CCC), provided input on trifluridine-tipiracil (Lonsurf) for the treatment of patients with metastatic colorectal cancer (mCRC).

To help capture the patient and caregiver experience, CCC conducted a national/international online survey from October 17th to October 27th, 2017. The survey comprised of dichotomous, multiple choice, likert scale, and open-ended questions; and the survey questions covered content on demographics, mCRC, its symptoms and their impact, experience with available treatments and new treatments including trifluridine-tipiracil, the relative importance of outcomes, as well as opinions on new drug access and funding. The survey was sent to 400 colorectal cancer (CRC) patients and caregivers residing in Canada, as well as patients in the United States and Europe. The number of international patients contacted about the survey is unknown. A total of 80 respondents completed the survey through Survey Monkey; respondents were comprised of 64 patients and 16 caregivers. Demographic information captured in the CCC survey results are summarized in Table 1.

Table 1: Demographic information of CCC survey respondents.

Demographic information	N (%) of respondents (total n=80)**
Country of residence	
Canada*	47 (59)
USA	30 (38)
Other	4 (3)
Age	
20-30	2 (3)
31-40	10 (13)
41-50	22 (28)
51-60	20 (25)
61-70	18 (23)
71-80	7 (9)
80+	1 (1)
Gender	
Male	20 (25)
Female	59 (75)
Stage of disease	
0	0
I	3 (4)
II	7 (9)
III	25 (31)
IV***	33 (41)
Notes: *Province of residence reported for the 47 (59%) Canadian survey respondents was as follows: ON (n=36, 77%), BC (n=5, 11%), NS (n=3, 6%), QC (n=2, 4%), and SK (n=1, 2%). **Not all respondents answered each survey question. ***Nine patients with stage IV disease were able to cite their experience with trifluridine-tipiracil.	

CCC had difficulty identifying and contacting mCRC patients and caregivers in Canada who could supply first-hand experience with trifluridine-tipiracil. Therefore, in addition to the national/international online survey, CCC also conducted an online outreach campaign directed to chat groups and forums throughout Canada and the U.S. Two CCC support group members also made an appeal on CCC's behalf. As a result of this outreach, CCC was able to conduct 11 in-depth

and high-quality telephone interviews with nine patients (one of whom is Canadian) and two caregivers. Demographic information captured in the CCC telephone interviews are summarized below in Table 2.

Table 2: Demographic information of CCC telephone interview respondents.

Demographic information	N (%) of respondents (total n=11)
Country of residence	
Canada*	1 (9)
USA	10 (91)
Age, range in years	41-81
Gender	
Male	2 (18)
Female	9 (82)
Stage of disease	
IV**	11 (100)
Notes: *Province of residence reported for Canadian patient respondent was BC. **All 11 respondents (9 patients and 2 caregivers) were able to cite their experience with trifluridine-tipiracil.	

Considering both the online survey and telephone interviews, CCC was able to gather information from a total of 73 patients (64 surveyed, 9 interviewed) and 18 caregivers (16 surveyed, two interviewed), 20 of whom (18 patients and 2 caregivers) had experience with trifluridine-tipiracil as treatment for mCRC. The information collected by patient interviews focused on respondent experience with trifluridine-tipiracil.

From a patient's perspective, there are a number of symptoms associated with mCRC that impact quality of life, which include fatigue, bloody stools, diarrhea or constipation, anemia, abdominal cramping, and bowel obstruction. Almost all CCC survey respondents (93%) reported they experienced symptoms from their CRC. Pain, diarrhea and fatigue resulting from the cancer were reported to be the most important and difficult to control symptoms. Most patients feel their CRC-induced symptoms interfere with their quality of life and their daily activities, citing they are not able to function "normally" in their family or work settings. Stomas and pain were identified as limitations exerting psychological impacts resulting from CRC; and respondents also noted experience with anxiety, depression and sleep problems. CCC noted CRC also significantly impacted the lives of caregivers who are fraught with enormous financial, physical and psychological challenges when caring for their loved ones. According to the survey and telephone interview results, the majority of patients accessed current combination chemotherapies such as FOLFOX, FOLFIRI and/or capecitabine with bevacizumab; other therapies, such as cetuximab, panitumumab, regorafenib, and pembrolizumab, were accessed much less frequently. Approximately half of respondents reported current therapies were effective at controlling their cancer-induced symptoms. Most patients cited fatigue, nausea, diarrhea, hair loss, vomiting, mouth sores, and hand and foot syndrome as being the most common side effects from these CRC treatments, with chemo-induced fatigue, nausea, and diarrhea identified as the most difficult to tolerate. Approximately half of survey respondents replied "yes" when asked if some of their needs were not being met by the current drugs available to treat their CRC. CCC indicated that for patients with refractory mCRC, limited therapeutic options exist to treat their disease, regardless of RAS mutational status; and the survey results clearly highlight patients' desire to be permitted access to therapies that will effectively control their disease with respect to overall survival, progression-free survival, and, in particular, improve quality of life. The 20 survey and interview respondents who had direct experience with trifluridine-tipiracil received the drug in multiple lines of therapy (first to sixth-line of treatment) and survey respondents indicated accessing the

drug either through a clinical trial, insurance plan, or self-pay. Patients cited manageable side effects with trifluridine-tipiracil that included fatigue, diarrhea, constipation, low blood counts, and abdominal discomfort, of which fatigue was considered the most difficult to tolerate. When asked to compare the side effects they experienced with trifluridine-tipiracil to other therapies they have taken, surveyed patient respondents reported milder/less side effects overall with trifluridine-tipiracil but noted issues with blood counts and fatigue. Interviewed respondents also noted better tolerance of trifluridine-tipiracil compared to other therapies. There were no survey respondents who rated their quality of life as low/severely impacted by trifluridine-tipiracil; all patients rated a 7 or greater on the 10-point scale (where 10 equates with high/normal living), demonstrating patients were able to achieve a high quality of life while on the therapy. Similar quality of life ratings were reported by the interview respondents.

Please see below for a summary of specific input received from CCC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

CCC reported that CRC is the second leading cause of cancer death in Canada in men and women combined. Improvements in the treatment of CRC have favourably affected patient outcomes such that the death rates have declined significantly in the past 20 years. Yet, a high proportion of patients with advanced stages will still die from this disease. CCC noted that statistics are particularly dire for people with mCRC; the five-year survival rate is less than 11% in this patient subgroup, and therefore additional treatment options are clearly needed.

3.2.1 Experiences Patients have with Metastatic Colorectal Cancer

CCC Online Survey

The majority of patient respondents experienced symptoms from their CRC (93%, 54/58 responses received). The CRC online patient survey results identified the following symptoms from CRC as the most prevalent:

- Fatigue (61%)
- Bloody stools (57%)
- Diarrhea (46%) or constipation (26%)
- Anemia (33%)
- Abdominal cramping (28%)
- Bowel obstruction (22%)

Pain, diarrhea and fatigue resulting from the cancer were reported to be the most important and difficult to control symptoms. The majority of patients seemed to feel their CRC-induced symptoms interfere with their quality of life and their daily activities; citing they are not able to function "normally" in their family or work setting:

- *"Not able to work, not able to volunteer, can't travel"*
- *"Can't really fulfill any part of life, family, exercise, work, etc*"
- *"I do not work regularly, because of bathroom issues"*
- *"Diarrhea limits social activities and so does fatigue"*
- *"Was not able to work or exercise or do housework or take care of kids."*

Stomas and pain were cited as limitations exerting psychological impacts resulting from CRC. Further, respondents also indicated experience with anxiety, depression and sleep problems:

- "*Stomas make you feel less than*"
- *"Problems associated with a colostomy, such as fear of odor, fear of leaking, trying to hide* colostomy from people knowing."
- "*pain limits mobility and QoL*"
- *"worry, anxiety, lack of focus"*
- *"Mind races. Can't sleep all night."*

3.2.2 Patients' Experiences with Current Therapy for Metastatic Colorectal Cancer

CCC Online Survey

According to the online survey results (49 responses received), the majority of patients accessed combination chemotherapies such as FOLFOX, FOLFIRI and/or capecitabine with bevacizumab to help reduce the burden of disease. Less than 12% of patient respondents accessed anti-epidermal growth factor receptor (EGFR) therapies such as cetuximab or panitumumab, and 10% accessed regorafenib. Fifty-six percent of respondents maintained these therapies were effective at controlling their cancer-induced symptoms. The most frequently cited side effects from these CRC treatments included fatigue, nausea, diarrhea, hair loss, vomiting, mouth sores, and hand and foot syndrome. Chemo-induced fatigue, nausea, and diarrhea were identified as the most difficult to tolerate. When patients were asked if some of their needs were not being met by the current drugs available to treat their CRC (49 responses received), 49% replied "yes" and furnished the following open-ended responses

- *"Deployment of Immunotherapies for MSS patients"*
- *"Third and fourth line options"*
- *"Need better access to clinical trials"*

Survey responses also highlighted the financial hardship or out of pocket expenses incurred by patients; 40% of respondents (20 out of 50 responses received) indicated they had to pay out of pocket for their medications/drugs, "*Had to pay for Xeloda, Emend, Lonsurf*".

CCC Interviews

Similar to the online survey, all 11 interview respondents (nine patients and two caregivers reporting on behalf of patients) indicated patients accessed combination chemotherapies such as FOLFOX, FOLFIRI, and/or capecitabine with bevacizumab. Fewer patients accessed EGFR therapies including cetuximab or panitumumab (2 patients), regorafenib (3 patients), and pembrolizumab or other immunotherapy (4 patients). No additional information was gathered on these treatments (i.e. side effects, needs met by drugs).

3.2.3 Impact of Metastatic Colorectal Cancer and Current Therapy on Caregivers

CCC Survey

The CCC online survey included 16 caregiver respondents. CCC noted CRC has also significantly impacted the lives of caregivers. Caregivers are fraught with enormous financial, physical and psychological challenges when caring for their loved ones:

- "*Loss of income, inadequate homecare and palliative supports, inadequate psychosocial support systems. "*
- *"Dealing with treatment-induced side effects, fear and uncertainty. Physically draining. More home duties. My inability to help make it better makes me feel helpless."*
- *"Days away from work to accompany spouse, stress of added responsibilities and worry for positive outcome"*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Trifluridine-tipiracil

CCC Survey

CCC noted that the survey results clearly highlight patients' desire to be permitted access to therapies that will effectively control their disease with respect to overall survival, progression-free survival, and, in particular, improve quality of life. Eighty-four percent of respondents (49 of 58 responses received) would be willing to take a drug that has been proven to provide better quality of life during their lifetime even if it does not extend overall survival by very much. Further, while 15% of respondents are willing to endure significant side effects for a two month survival benefit, almost 50% are willing to endure those same significant toxicities for a one year survival benefit.

3.2.2 Patient Experiences to Date with Trifluridine-tipiracil

CCC Survey

CCC indicated that for patients with refractory mCRC, limited therapeutic options exist to treat their disease, regardless of RAS mutational status. The therapy under review, trifluridine-tipiracil, could help address this unmet medical need by providing patients with a new therapeutic option that has an acceptable toxicity profile and that can help extend their overall survival. Trifluridine-tipiracil is a convenient, orally administered treatment that may allow patients to continue their journey with refractory mCRC in the third- (if RAS mutant) or fourth-line (if RAS Wild Type) setting. Access to trifluridine-tipiracil could make a significant difference in the lives of patients who have exhausted standard of care therapies.

The CCC survey results identified nine patients who had experience with trifluridine-tipiracil as first-, second-, fourth- and sixth-line treatment of mCRC. These patients accessed the drug either through a clinical trial, insurance plan, or self-pay.

Six of the nine patient respondents reported that the drug was able to shrink/contain their mCRC. Patients cited fatigue, nausea, neutropenia, anemia, diarrhea and abdominal pain as the most prevalent treatment-induced side-effects, of which fatigue was considered the most difficult to tolerate. When asked to compare the side effects they experienced with trifluridine-tipiracil to other therapies they have taken, patients reported milder/less side effects overall with trifluridine-tipiracil but noted issues with blood counts and fatigue.

There were no patient respondents who rated their quality of life as low/severely impacted by trifluridine-tipiracil; all patients rated a 7 or greater on the 10-point scale (where 10 equates with high/normal living), demonstrating patients were able to achieve a high quality of life while on the therapy. Eighty-eight percent of patient respondents rated their overall experience with trifluridine-tipiracil as "much better" when compared to

other treatments accessed for their mCRC, and all nine respondents maintained the therapy should receive a positive funding recommendation because:

- *"Any chance to prolong a patient's life with such mild side effects should be allowed"*
- *"Everyone deserves a chance at living longer with cancer"*
- *"Potential for controlling cancer progression and extending life expectancy with minimal side effects"*
- *"New drugs are needed and this could help someone"*
- *"My father has been fighting CRC since 2009. Lonsurf kept him stable for 13 months. We are very grateful for this drug because of its minimal side effects and schedule"*

CCC Interviews

As noted above, CCC conducted extensive telephone interviews with nine patients and two caregivers (reporting on behalf of patients) who accessed trifluridine-tipiracil in either Canada or the U.S. through clinical trials, insurance and self-pay. Patient respondents had experience with the drug as second- through to seventh-line of therapy. Two patients interviewed are currently receiving the drug as treatment for their mCRC. The number of cycles of trifluridine-tipiracil received by all patient respondents ranged from two to 12.

Overall, survey respondents identified trifluridine-tipiracil as an important treatment option for progressing CRC, with manageable side effects that included fatigue and nausea (both described as mild), diarrhea, constipation, low blood counts, and abdominal discomfort. When asked to rate their quality of life on trifluridine-tipiracil, patient ratings (1=low and 10=high quality of life) ranged from 7 to 10. Patients provided comments related to their ratings:

- *"It was really ok to tolerate – way easier to tolerate compared to others like oxaliplatin, that's for sure."*
- *"Was able to go on vacation and did most day to day things for my family. Compared to previous therapies, like FOLFOX or FOLFIRI, not that bad at all. I could eat and I took a girls' getaway, road trips with my friends and went to parties."*
- *"I could take care of my 2 young kids and grocery shop, clean the house and most everything I was doing before I became ill, except go back to work."*
- *"His quality of life was really good. His regular day to day living was almost normal while on Lonsurf. He was his regular self in comparison to the other chemos. The Lonsurf was really easy to tolerate. He bathed and dressed himself. Drove, worked around the house a bit."*

3.3 Additional Information

The CCC survey asked respondents why access to trifluridine-tipiracil is so important. Respondents provided thoughtful replies and underscored the need for new treatment options for patients with refractory mCRC: "Any additional therapies to extend a stage IV patient's lifespan" and "It is important that new therapies be provided…". Specifically, patients and caregivers identified the following unmet needs: the need for a novel, conveniently administered oral therapy, with an acceptable toxicity profile that has the potential to improve overall survival in the refractory population. Our surveyed population and interviewed population all agree that trifluridine-tipiracil was able to provide them with disease control (either complete response, partial response or stable disease), minimal side effects, and a conveniently administered therapy that could be delivered in

the comfort of their own homes. No patients reported discontinuing the therapy due to drug-related toxicity. If publicly funded, trifluridine-tipiracil could be an extremely important therapeutic option for the mCRC patient population who have exhausted standard of care therapies or are not considered candidates for those therapies. We, therefore, strongly support and urge that a positive funding recommendation be issued for trifluridine-tipiracil for the treatment of mCRC. We believe trifluridine-tipiracil aligns well with the identified patient and caregiver need for a new, effective treatment option that is capable of maintaining a high quality of life.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from seven provinces (Ministries of Health and/or cancer agencies) and federal drug program participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- The value of trifluridine-tipiracil given the very modest overall survival, short progression-free survival, low objective response rates and occurrence of serious adverse events

Economic factors:

- Cost of supportive therapy (e.g. anti-emetics, granulocyte colony-stimulating factor)
- Resources required to monitor and treat serious adverse events

Please see below for more details.

4.1 Currently Funded Treatments

Currently, there are no funded treatment options for mCRC after chemotherapy, although for patients who have RAS wild type tumors, treatment with an EGFR inhibitor is available. Best supportive care is available for all patients, or for patients who have private drug insurance, regorafenib is an option.

4.2 Eligible Patient Population

There is an unmet need for this group of patients and the younger patients often seek further treatments. However, the clinical benefits of trifluridine-tipiracil are quite low (an incremental 1.8 months in median overall survival, an incremental 0.3 months of progression free survival, a low objective response rate and a number of serious adverse effects). PAG noted that trifluridine-tipiracil and regorafenib are indicated for the same group of patients. pERC did not recommend funding of regorafenib as it had only a very modest progression-free survival and overall survival benefit, moderate but not insignificant toxicities, and a similar decline in quality of life.

As there is no direct comparison with intravenous chemotherapy, PAG is seeking clarity that trifluridine-tipiracil would be the last line of therapy, after patients have exhausted all treatment options.

PAG noted that the trial included only patients with ECOG performance status of 0 to 1. In practice, there would be many patients who would have ECOG performance status of 2 at this stage. PAG has concerns of extending treatment to patients with performance status of 2, given the number of serious adverse events associated with trifluridine-tipiracil. If trifluridine-tipiracil is recommended for reimbursement, PAG suggests treatment be limited to patients with ECOG performance status of 0 to 1, aligning with trial eligibility.

Patients with metastatic small bowel cancer are often treated similarly to patients with metastatic large bowel cancer. PAG is seeking information on the generalizability of the results to patients with metastatic small bowel cancer.

4.3 Implementation Factors

Additional resources are required to monitor and treat severe (grade 3 to 4) myelosuppression including anemia, neutropenia, thrombocytopenia and febrile neutropenia. The cost of supportive therapy (e.g. anti-emetics, G-CSF) also needs to be considered in implementation.

Trifluridine-tipiracil is available in two strengths and dose is based on body surface area. PAG noted that some patients will require two different strengths of tablets to make up their dose and thus, may have two dispensing fees in those provinces where the access to oral therapies is through pharmacare.

4.4 Sequencing and Priority of Treatments

PAG noted that trifluridine-tipiracil would be the last line of therapy after chemotherapy. For patients who have RAS wild type mCRC, treatment with an EGFR inhibitor is available and PAG is seeking guidance on sequencing of EGFR inhibitors and trifluridine-tiparacial in this group of patients. Regorafenib for mCRC is not funded in any province give the negative pERC recommendation.

4.5 Companion Diagnostic Testing

None required.

4.6 Additional Information

PAG noted that the blister packaging of the tablets is an enabler to implementation as it would minimize drug wastage and also minimize exposure of hazardous drugs to health care providers and caregivers.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided from total of 13 oncologists representing two groups.

The clinicians providing input identified that although regorafenib is approved for metastatic colorectal cancer after previous chemotherapy, regorafenib is not funded in any province. They indicated that trifluridine-tipiracil (TAS-102) provides a treatment option that appears to be better tolerated than regorafenib. They noted that the number of patients who would be eligible to receive would be small relative to the incident population. Please see below for details from the clinician inputs.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for this Type of Cancer

The clinicians providing input noted that there are no funded treatment options for this group of patients at the present time. Regorafenib has shown evidence of a survival benefit in this population of patients but is not funded in any Canadian jurisdictions due to unfavourable cost-benefit analysis. Checkpoint inhibitors have shown significant benefit in MSI-H patients, but again are not funded. Clinical trials remain a viable option for a select group of patients.

5.2 Eligible Patient Population

Colorectal cancer is the second cause of cancer-related death in men, and third cancer-related death in women in Canada. Each year, approximately 9,400 Canadians will die from this disease (Canadian Cancer Statistics, 2017). Patients with metastatic colorectal cancer will be treated with palliative chemotherapy, bevacizumab and cetuximab/panitumumab if they are RAS wild type. However, almost all of these patients will progress on these treatments. For patients with progressed disease, there are no treatment options, except clinical trials since regorafenib is not publicly funded in Canada. TAS-102 is the only option for these patients.

The clinicians indicated that the proportion of patients diminishes as each line of therapy becomes exhausted, and patients who have failed available therapies do not survive for a sufficient duration of time to increase disease prevalence. Thus, the number of patients eligible for further treatment with TAS-102 would be small.

There are no obvious subgroups that should be excluded at the present time. However, the trial was published over 2 years ago and since that time there has been evidence of treatment benefit using checkpoint inhibitors, particularly in MSI-H patients. In this subset, it is not known whether TAS-102 provides a survival benefit.

5.3 Identify Key Benefits and Harms with New Drug Under Review

The key benefits identified include survival prolongation and delay time to deterioration of performance status. The key side effects from TAS-102 include neutropenia or febrile neutropenia.

The clinicians providing input also identified that patients should not receive TAS-102 if they have poor performance status (ECOG 2-4), impaired bone marrow, hepatic or renal functions, or have not progressed on previous chemotherapy as indicated.

5.4 Advantages of New Drug Under Review Over Current Treatments

The clinicians providing input noted that although TAS-102 has not been directly compared to

regorafenib, regorafenib is not widely used due to its side effect profile and is not a funded in any province. TAS-102 potentially offers a more tolerable treatment option for these patients. This patient population has an unmet need in that there are no other standard funded options.

The drug is convenient as an oral agent, and provides a meaningful survival benefit to the patient population. Tolerability and quality of life preservation provide additional assurance of benefit and safety.

5.5 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians providing input identified that TAS-102 will be used in patients who have progressed on currently available therapies including 5-FU/oxaliplatin/irinotecan containing cytotoxic chemotherapy, bevacizumab and anti-EGFR therapy if appropriate. TAS-102 is likely to replace regorafenib given its perceived better tolerated side effect profile. Most patients will likely be treated with TAS-102 followed by regorafenib, if available.

5.6 Companion Diagnostic Testing

Not needed.

5.7 Additional Information

None.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of trifluridine-tipiracil (Lonsurf) in patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti VEGF therapy, and if KRAS wild-type, anti EGFR therapy. Appropriate comparators and outcomes of interest are summarized in Table 3 in section 6.2.1.

A Supplemental Question and relevant to the pCODR review and to the Provincial Advisory Group was identified while developing the review protocol and is outlined in section 7. Of note, regorafenib is not currently publically funded in any provinces.

- Critical appraisal of the findings of a systematic review and network meta-analysis comparing the efficacy and safety of trifluridine-tipiracil to regorafenib[56].

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCT§	Adult patients (≥18 years) with recurrent mCRC previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti VEGF therapy, and if KRAS wild-type, anti EGFR therapy. Subgroup: • Patients with rectal cancer who have received pelvic radiation therapy	Trifluridine-tipiracil (Lonsurf)	• BSC • placebo • regorafenib • Immunotherapeutic approaches	• **OS** • **PFS** • **HRQoL** • ORR • Metastases resection rate • AE • SAE • WDAE

[Abbreviations] **AE** - adverse events; **BSC**- best standard care; **EGFR** - epidermal growth factor; **mCRC** - metastatic colorectal cancer; **ORR** - objective tumour response rate; **OS** - overall survival; **PFS** - progression-free survival; **RCT**- randomized controlled trial; **ROA** - route of administration; **SAE** - serious adverse events; **HRQoL** - health related quality of life; **VEGF** - vascular endothelial growth factor; **WDAE** -withdrawal due to adverse events.

* *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

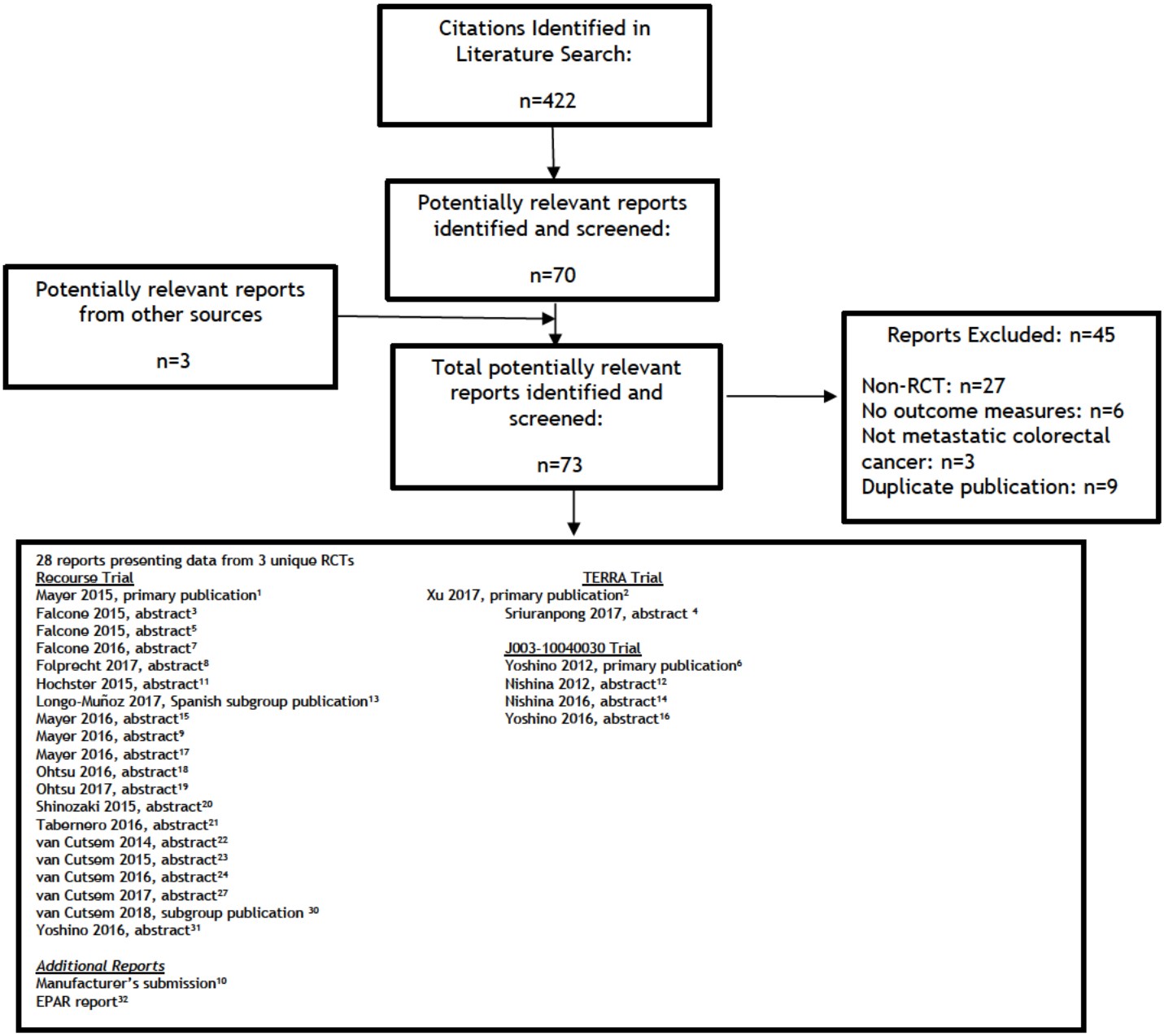
§ *Includes retrospective and exploratory analyses from prospective randomized controlled trials.*

6.3 Results

6.3.1 Literature Search Results

Of the 73 potentially relevant reports identified, 28 studies were included in the pCODR systematic review[1-24,27,30-32] and 45 studies were excluded. Studies were excluded because they were non-RCT[54,55,57-81] outcomes were not relevant[82-87], patient population was not relevant[88-90], or they were duplicates[17,19,23,91-96].

Figure 1. Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to RECOURSE, TERRA, and J003-10040030 were also obtained through requests to the Submitter by pCODR[10].

6.3.2 Summary of Included Studies

Three randomized control trials met the eligibility criteria[1,2,6]. Study characteristics of these trials are summarized in Table 4 and quality assessment results are presented in Tables 5 and 8.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
RECOURSE Trial[1,3,5,8-11,13,15,17-24,27,30,31]				
Clinical trial NCT01607957 Double blind, two-arm, parallel-group, phase 3 RCT Patient enrollment: June 2012- October 2013 N randomized= 800 Multicentre (101 centres in 13 countries) Randomized 2:1 ratio, stratified by: •KRAS status (wild-type, mutant) •Time since diagnosis of first metastasis (< or >18months) •Geographic region (Asia-Japan, Western-Australia, Europe, US) Funded by Taiho Oncology Inc. - Taiho Pharmaceutical Co., Ltd.	Key Inclusion Criteria: •18≥ years of age • Histologically or cytologically confirmed adenocarcinoma of the colon or rectum •Received at least 2 prior standard chemotherapy regimens for mCRC and was refractory, intolerant or failing them •ECOG PS of 0-1 at baseline and on day 1 of cycle 1 •Able to take medication orally •Have metastatic lesion(s) •Adequate organ function •Known KRAS status Exclusion Criteria: •Serious comorbidities including brain or leptomeningeal metastasis •Treatment within specified time frames prior to study drug administration •Previous treatment with trifluridine-tipiracil	Trifluridine-tipiracil 28-day treatment cycle + BSC Days 1-5; 8-12: 35mg/m2/dose bd Days 6-7; 13-28: Rest Given until disease progression, voluntary study withdrawal, or unacceptable toxicity	Placebo 28-day treatment cycle + BSC (same schedule as intervention arm)	Primary: •OS Key Secondary: •PFS •Safety and tolerability, AEs and SAEs Other Secondary: •TTF •ORR •DCR •DR •Subgroup analysis by KRAS and BRAF status on OS and PFS •ECOG PS •European subgroup analysis on OS, PFS, and hospitalization •Timing of AE and SAE analysis •Previous regorafenib treatment subgroup analysis on OS and safety •Spanish subgroup analysis on OS and PFS •Impaired renal and hepatic subgroup analysis on AE/SAE and OS •Supportive therapy use analysis

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
RECOURSE Trial[1,3,5,8-11,13,15,17-24,27,30,31]				
	•Unresolved toxicity to prior therapies (≥Grade 2) •Pregnancy or lactation			•Neutropenia onset analysis on survival benefit •Geographic subgroup analysis on efficacy, safety, and hospitalization •AE analysis on QoL and duration of treatment •Age subgroup analysis on OS and PFS •Exposure subgroup analysis on SAE •Lines of prior treatment subgroup analysis on HR for OS
TERRA[2,4,10]				
Clinical trial NCT01955837 Double blind, two-arm, parallel-group, phase 3 RCT Patient enrollment: October 2013-June 2015 N randomized: 406 Multicentre (30 sites in 3 countries) Randomized 2:1 ratio, stratified by: •KRAS status (wild-type or mutant) •Country (China, Republic of Korea or Thailand)	Key Inclusion Criteria: •18≥ years of age • Histologically or cytologically confirmed adenocarcinoma of the colon or rectum •Received at least 2 prior standard chemotherapy regimens for mCRC and was refractory, intolerant or failing them •ECOG PS of 0-1 •Able to take medication orally •Have metastatic lesion(s) •Adequate organ function •Known KRAS status Exclusion Criteria:	Trifluridine-tipiracil 28-day treatment cycle + BSC Days 1-5; 8-12: 35mg/m2/dose bd Days 6-7; 13-28: Rest Given until disease progression, voluntary study withdrawal, or unacceptable toxicity	Placebo 28-day treatment cycle + BSC (same schedule as intervention arm)	Primary: •OS Secondary: •KRAS and number of prior treatment regimens subgroup analysis on OS •PFS •TTF •ORR •DCR •DR •Safety evaluation-AEs Other Secondary: •Country subgroup analysis on efficacy and safety

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
RECOURSE Trial[1,3,5,8-11,13,15,17-24,27,30,31]				
Funded by Taiho Pharmaceutical Co., Ltd.	•Serious comorbidities including brain or leptomeningeal metastasis •Treatment within specified time frames prior to study drug administration •Previous treatment with trifluridine-tipiracil •Unresolved toxicity to prior therapies (≥Grade 2) •Pregnancy or lactation			
J003-10040030[6,10,12,14,16]				
Clinical trial CTI090880 Double blind, two-arm, parallel-group, phase 2 RCT Patient enrollment: August 2009-April 2010 N randomized: 172 Multicentre- 20 sites in Japan Randomized 2:1 ratio, stratified by: •Baseline ECOG PS (0-3) Funded by Taiho Pharmaceutical Co., Ltd.	Key Inclusion Criteria: •≥20 years of age • Histologically or cytologically confirmed adenocarcinoma of the colon or rectum •Received at least 2 prior standard chemotherapy regimens for mCRC and was refractory, intolerant or failing them •ECOG PS of 0-2 •Able to take medication orally •Have measurable metastatic lesion(s) •Adequate organ functioning Exclusion Criteria: •Serious comorbidities including brain metastasis	Trifluridine-tipiracil 28-day treatment cycle + BSC Days 1-5; 8-12: 35mg/m2/dose bd Days 6-7; 13-28: Rest Given until disease progression, voluntary study withdrawal, or unacceptable toxicity	Placebo 28-day treatment cycle + BSC (same schedule as intervention arm)	Primary: •OS Secondary: •PFS •Objective response •DC •DR •TTF •Efficacy analysis by KRAS status and AEs •Neutropenia onset analysis on survival benefit •Risk group subgroup analysis on OS and PFS

Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
RECOURSE Trial[1,3,5,8-11,13,15,17-24,27,30,31]				
[Abbreviations] AE - adverse event; bd- twice daily; BSC - best standard care; DCR - disease control rate; DR- Duration of response; ECOG PS - Easter Cooperative Group Performance Status; KRAS - Kirsten Rate Sarcoma Oncogene; mCRC - metastatic colorectal cancer; OS - overall survival; ORR - overall response rate; PFS - progression-free survival; RCT - randomized controlled trial; SAE - serious adverse event; TTF - time to treatment failure; QoL - quality of life				

Table 5: Select quality characteristics of included studies of trifluridine-tipiracil in patients with mCRC

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
RECOURSE	Trifluridine-tipiracil vs. Placebo	OS	571[A]	800	Central Randomization	Yes	Yes[B]	Yes	Yes	No	Yes
TERRA	Trifluridine-tipiracil vs. Placebo	OS	288[C]	406	Minimization Method	Yes	Yes[B]	Yes	Yes	No	Yes
J003-10040030	Trifluridine-tipiracil vs. Placebo	OS	121[D]	172	Central Randomization	Yes	Yes[B]	No[E]	Yes	No	Yes

[Abbreviations] ITT - intention to treat; OS - overall survival.
A: 571 death events were expected to provide 90% power for OS HR detection of 0.75 with a one-sided type I error rate of 0.025
B: Patients, investigators, ancillary trial personnel, and the sponsor were blinded to treatment assignment
C: 288 death events were expected to provide 90% power for OS HR detection of 0.67 with a one-sided type I error rate of 0.025
D: 121 death events were expected to provide 80% power for OS HR detection of 0.67 with a one-sided type I error rate of 0.1
E: Two patients were excluded from efficacy analyses, one for a major protocol violation and another because they didn't receive stud medication

a) Trials

Three randomized controlled trials, RECOURSE[1], TERRA[2], and J003-10040030[6], were included in this review.

RECOURSE and TERRA were phase III clinical trials and J003-10040030 was a phase II clinical trial. All were randomized, double-blind, two-arm, parallel group, and placebo-controlled studies. Crossover was not allowed in any of the trials[10]. No Canadian sites were included in any of the three studies. The patient population in all three studies were previously treated mCRC patients, 18 years of age or older in RECOURSE and TERRA, 20 years of age or older in J003-10040030. All groups in each trial received best supportive care (BSC) alongside treatment. The

randomization ratio was 2:1 for all studies. Major patient inclusion and exclusion criteria are summarized in Table 4.

All studies were multi-centred trials, RECOURSE included 101 sites from 13 countries, TERRA included 30 sites from three countries, and J003-10040030 included 20 sites from Japan. RECOURSE and TERRA included patients with an ECOG PS of 0-1 while J003-10040030 included patients with an ECOG PS of 0-2. KRAS status was required for inclusion in RECOURSE and TERRA, but not J003-10040030. KRAS status was tested and reported for 88% of J003-10040030 patients.

TERRA and J003-10040030 randomized using a minimisation method and stratified based on KRAS status and country, and baseline ECOG status, respectively. RECOURSE randomized using a dynamic allocation method and stratified based on KRAS status, time since first metastasis, and geographic region.

All three trials used a superiority trial design. The primary outcome for all trials was overall survival (OS). RECOURSE was designed to have 90% power to detect a hazard ratio (HR) of 0.75 for trifluridine-tipiracil versus placebo with a one-sided type I error rate of 0.025. This required 800 patients to enroll and at least 571 events (deaths) to occur. TERRA had 90% power and J003-10040030 had 80% power to detect a HR of 0.67 with one sided type I error rates of 0.025 and 0.1 respectively. This required 400 patients to enroll and 288 events to occur for TERRA and 162 patients to enroll and 121 events to occur for J003-10040030. A two-sided, stratified log-rank test with a significance level of 0.05 was used in efficacy outcome analyses of RECOURSE and TERRA. J003-10040030 used a stratified log-rank test with a significance level of 0.1 for efficacy outcome analyses. Hazard ratios and confidence intervals were calculated using Cox proportional hazards model in all trials. RECOURSE and TERRA reported 95% confidence intervals and J003-10040030 reported 80% confidence intervals corresponding to the significance level and 95% confidence intervals. None of the trials indicate early termination occurred. Secondary outcomes of all trials included progression free survival (PFS), objective tumor response rate (ORR), time to treatment failure (TTF), safety based on adverse events (AEs), and disease control rate (DCR). PFS and TTF were assessed using log rank tests and ORR and DCR were assessed using fisher's exact tests.

All three trials were double-blinded, the investigators, patients, and ancillary trial personnel were all blind to treatment assignment. Trial sponsor employees were blinded except for pre-specified personnel involved in Pharmacovigilance reporting activities and drug labelling and distribution. The funding for all three trials came from Taiho Pharmaceutical Co., Ltd.

RECOURSE included three amendments to their global protocol and five country specific amendments at the primary analysis cut-off date. Overall, 5.4% of patients treated with trifluridine-tipiracil and 6.8% of patients treated with placebo, had at least one study period or entry criteria violation[10]. Patient data was censored to the date of violation for analysis. For TERRA, there were two protocol amendments: 1) to clarify descriptions and definitions of: HIV, HIV tests, baseline assessments, the drug name (tipiracil hydrochloride), a prior study number, inclusion/exclusion criteria and prohibited medications, patient numbering scheme, the study periods, statistical analyses, the publication policy and the sponsor name; and 2) to clarify and correct descriptions of: the statistical analysis, a spelling error, patient population, and remove a redundant reference[10]. For J003-10040030, protocol deviations occurred for 17 (14.9%) patients in the trifluridine-tipiracil group and 7 (12.1%) patients in the placebo group[10]. In the trifluridine-

tipiracil group, 10 patients had a deviation from laboratory study/observation schedules, four patients had a deviation from the study regimen, two patients had a deviation from the defined dose, one patient had a deviation related to obtaining consent for PGX, and one patient had a deviation from the exclusion criteria. All seven patients in the placebo group had a deviation from laboratory study/observation schedules.

b) Populations

Population characteristics of all three included studies are summarized in Table 6. For all three studies, patient characteristics at baseline were similar between trifluridine-tipiracil and placebo groups.

Of the 1002 patients screened for participation in the RECOURSE study, 800 were randomized in a 2:1 ratio receiving trifluridine-tipiracil (n=534) or placebo (n=266). The median age was 63 years with a range of 27-82 years and the proportion of males was 61% for treatment and 62% for placebo. The majority of the patients were white (58%), had 18 months or more from diagnosis of metastasis (79%), and on fourth or greater line of treatment (61%)[1,10].

TERRA randomized 406 eligible patients of the 516 screened in a 2:1 ratio receiving trifluridine-tipiracil (n=271) or placebo (n=135). The median age was 57 years with a range from 24-81 years and the proportion of males was 63% for treatment and 62% for placebo. All patients were Asian, the majority were KRAS wild-type (63%), and had an ECOG PS of 1 (77%)[2].

J003-10040030 screened 173 patients and randomized 169 of them in a 2:1 ratio receiving trifluridine-tipiracil (n=112) or placebo (n=57). The median age was 63 years with a range of 28-80 years and the proportion of males was 57% for treatment and 49% for placebo. The majority of patients had and ECOG PS of 0 (63%), and were on third or greater line of treatment (82%). Notably, J003-10040030 included patients with an ECOG status of 2 (2%)[6].

Table 6: Patient Characteristics

	RECOURSE[1]		TERRA[2]		J003-10040030[6]	
	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo
N randomized	534	266	271	135	112	57
Age (yrs)						
Median	63	63	58	56	63	62
Range	27-82	27-82	26-81	24-80	28-80	39-79
Sex (%)						
Male	61	62	63	62	57	49
Female	39	38	37	38	43	51
ECOG performance Status (%)						
0	56	55	24	22	64	61
1	44	45	76	78	33	37
2	0	0	0	0	3	2
Primary site of disease (%)						
Colon	63	61	57	63	56	63
Rectum	37	39	43	37	44	37
KRAS Mutation (%)						
Wild type	49	49	63	63	55	48
Mutant	51	51	37	37	45	52

	RECOURSE[1]		TERRA[2]		J003-10040030[6]	
	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo
Time since cancer diagnosis, median (months)	36	39	22.8	26.3	NR	NR
Time from Diagnosis of metastases (%)						
<18 mo	21	21	49	39	10	18
≥18 mo	79	79	51	62	87	83
Number of metastatic sites (%)						
1-2	58	55	61	61	60	54
≥3	42	45	39	39	39	46
Number of prior regimens (%)						
2	18	17	23	19	15	23
3	22	20	27	27	85	77
≥4	60	63	50	55		
Previous Treatment (%)						
Bevacizumab	100	99.6	19	20	78	82
Cetuximab/Panitumumab	52.1	54.1	17	19	63*	63*

*NR: Not reported; * Only cetuximab*

c) Interventions

In all three trials patients received oral trifluridine-tipiracil at 35mg/m^2/dose or placebo twice daily after morning and evening meals over days 1-5 and 8-12 in each 28 day cycle. The other days were periods of rest. Best supportive care was received by all patients. Treatment continued until tumor progression, withdrawal of consent, unacceptable toxicity, or death. Both RECOURSE and TERRA also include physician's discretion as a discontinuation criteria[1,2,6,10].

Dose reduction protocol in cases of toxicity was also specified in each study. No dose increases were permitted. RECOURSE and TERRA allowed for a maximum of three dose reductions in 5mg/m^2 steps. J003-10040030 allowed for a dose decrease of 10mg/day as needed. A total of 73 (14%) patients in the trifluridine-tipiracil group required dose reductions. Single dose reductions occurred in 53 patients (10%), two reductions occurred in 18 (3%) patients, and three occurred in two (<1%)[10]. In TERRA at least one dose reduction occurred in 23 (8.5%) patients in the treatment arm and one (0.7%) patient in the placebo arm. No dose reductions occurred in the placebo arm for J003-10040030 and 22 (20%) patients in the treatment arm had at least one dose reduction. Treatment interruptions occurred in all studies, in RECOURSE they occurred in 245 (52.6%) patients in the treatment group and 14 (6.5%) in the placebo group. In TERRA interruptions occurred in 153 (65.9%) patients in the treatment group and five (4.6%) patients in the placebo group. In J003-10040030 interruptions occurred in 35 (31.3%) patients in the treatment group and six (10.5%) patients in the placebo group.

Anticancer therapies, beyond the therapy being investigated, were not permitted during the study period. Concomitant therapy for general treatment of major adverse drug reactions was permitted in J003-10040030. RECOURSE and TERRA allowed for concomitant use of antiviral drugs that are human thymidine kinase substrates with caution, haematological support (e.g. blood transfusion and granulocyte colony stimulating factors (G-CSF)), anti-diarrhoeal therapy, and antiemetic therapy. Granulocyte colony stimulating factor (G-CSF) is used in the treatment of neutropenia. G-CSF was administered in 9.4% of treatment patients and no placebo patients in RECOURSE and 14.2% of treatment patients and no placebo patients in J003-10040030[10]. In TERRA (J003-1004090) 100 (36.9%) patients

in the LONSURF group and 1 (0.7%) patients in the placebo group received G-CSF[10]. Based on the collection of the specific data in the TERRA study, it is not clear whether patients received G-CSF therapy for therapeutic or preventive purposes[10]. At least one concomitant medication was used in 98.9% of treatment patients and 98.1% of placebo patients in RECOURSE. In TERRA 90.4% of treatment patients and 81.5% of placebo patients used concomitant medication. J003-10040030 had 17.0% of patients in the treatment arm and 10.5% of patients in the placebo arm use concomitant medication.

RECOURSE patients received 89% of the targeted dose for a mean (±SD) duration of 12.7±12.0 weeks in the trifluridine-tipiracil group and 95% of the targeted dose for a mean duration of 6.8±6.1 weeks in placebo. Mean number of cycles initiated were 3.4±2.56 in the trifluridine-tipiracil group and 2.3±1.49 in the placebo group. Mean dose intensities were 155.1±20.0 mg/m^2/wk in the trifluridine-tipiracil group and 165.3mg/m^2/wk in the placebo group. Of 466 patients that initiated at least two cycles, 52.6% experienced an interruption of four or more days.

TERRA patients received 98.2% of the targeted dose for a mean duration of 14.93±12.20 weeks in the trifluridine-tipiracil group and 100% of the targeted dose for a mean duration of 8.76±4.38 weeks in the placebo group. Mean number of cycles initiated were 3.5±2.77 in the trifluridine-tipiracil group and 2.2±1.08 in the placebo group. Median dose intensities were 165.6 mg/m^2/wk in the trifluridine-tipiracil group and 167.8 mg/m^2/wk in the placebo group. Of 232 patients that initiated at least two cycles, 65.9% experienced an interruption of four or more days.

The dose intensity after initial dose in the trifluridine-tipiracil group was 147 mg/m^2/wk at 85.7% of the targeted dose in the J003-10040030 study. Mean duration of treatment was 35 days in the trifluridine-tipiracil arm and 16 days in the placebo arm[10]. Mean number of treatment cycles initiated was 3.6±3.0 in the trifluridine-tipiracil group and 1.7±1.0 in the placebo group[10]. Treatment interruption was required in 31% of patients in the trifluridine-tipiracil group lasting a median length of seven days.

d) Patient Disposition

Patient disposition is summarized for all trials in Table 7.

In the RECOURSE trial 1002 patients were assessed for eligibility, 800 of which were enrolled and randomized. Of the randomized patients two did not receive study medication, one in the trifluridine-tipiracil group and one in the placebo group. There were three populations included for analysis, intent to treat (ITT), as treated (AT), and tumor response (TR). Eight-hundred patients were included in the ITT population, 798 in the AT population and 760 (95%) in the tumor response (TR) population. Primary efficacy analysis used the ITT population and safety analysis used the AT population. Discontinuation of study treatment occurred in 496 (92.9%) and 263 (98.9%) patients in the trifluridine-tipiracil and placebo arm respectively. The main reason for discontinuing treatment was radiologic progression (n=638). Six patients were lost to follow up, three in each group. A total of 574 patients died by the OS analysis cut-off date of January 24th, 2014. Three patients in the trifluridine-tipiracil arm and two in the placebo arm were still being treated at the January 31st, 2014 cut-off date[1,10]. After trial discontinuation 224 patients in the trifluridine-tipiracil arm and 118 patients in the placebo arm received further cancer treatment. Patients received either surgery (trifluridine-tipiracil-1%; placebo 2%), systemic therapy (trifluridine-tipiracil-42%; placebo 43%), or investigational drugs (trifluridine-tipiracil-4%; placebo 5%). Regorafenib was

included in post-study anti-tumour therapy regimens for 84 patients in the trifluridine-tipiracil group and 41 patients in the placebo group[32].

In the TERRA trial, 516 patients were assessed for eligibility, 406 of whom were enrolled in the trial and randomized. All randomized patients received at least one dose of treatment. There were three populations included for analysis, ITT, AT, and TR. Four-hundred and six patients were included in the ITT and AT populations and 391 (96%) in the TR population. Primary efficacy analysis used the ITT population, other efficacy analyses used the TR population. Study treatment was discontinued in 264 (97.4%) and 135 (100%) patients in the trifluridine-tipiracil and placebo arm respectively. Two patients in the trifluridine-tipiracil arm were lost to follow up. The main reasons for discontinuation were radiologic progression (n=323) and adverse events (n=35). A total of 316 patients died by end of trial. After trial discontinuation, some patients continued treatment with biological therapy (trifluridine-tipiracil-14%; placebo 16%), chemotherapy (trifluridine-tipiracil-14%; placebo 20%), or investigational drugs (trifluridine-tipiracil-14%; placebo 16%)[10]. Biological therapy included anti-vascular endothelial growth factor (VEGF) agents, cetuximab, and chemotherapeutic agents. Chemotherapy only included chemotherapeutic agents[2].

In J003-10040030 172 patients were assessed for eligibility, enrolled, and randomized. One patient in either group did not receive treatment. There were two populations included for analysis, AT and efficacy. The AT population was used for safety analysis and included all patients that had received at least one dose of treatment (trifluridine-tipiracil n=113; placebo n=57). The efficacy population included patients that had received at least one dose of treatment and had not violated study protocol (trifluridine-tipiracil n=112; placebo n=57). The patient excluded for study protocol violation had been taking a prohibited concomitant treatment. One-hundred and nine (95.6%) and 57 (100%) patients in the trifluridine-tipiracil and placebo arm, respectively, discontinued study treatment. The main reason for treatment discontinuation was disease progression (98%). A total of 123 patients died by end of trial. After trial discontinuation 46 patients in the trifluridine-tipiracil arm and 26 patients in the placebo arm received further cancer treatment. Those patients received fluoropyrimidine-based treatment (trifluridine-tipiracil-28%; placebo 37%), irinotecan-based treatment (trifluridine-tipiracil-7%; placebo 21%), oxaliplatin-based treatment (trifluridine-tipiracil-12%; placebo 18%), bevacizumab (trifluridine-tipiracil-12%; placebo 21%), or anti-VEGF agents (trifluridine-tipiracil-11%; placebo 9%)[6].

Table 7: Patient Disposition

	RECOURSE[1,10]		TERRA[2]		J003-10040030[6]	
	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo
Patients Assessed	1002		516		172	
Patients Randomized	534	266	271	135	114	58
Patients Treated	533	265	271	135	113	57
Study Discontinuation	496	263	262	135	109	57
• Radiological Progression	416	222	212	111		

	RECOURSE[1,10]		TERRA[2]		J003-10040030[6]	
	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo	Trifluridine-tipiracil	Placebo
• Clinical Disease Progression	33	31	12	6	99	56
• Adverse Event/Serious Adverse Event	19	4	24	11	4	1
• Death	7	4	NR	NR	NR	NR
• Withdrawal of Consent	12	1	8	5	NR	NR
• Physician's Decision	NR	NR	NR	NR	1	0
• Protocol Violation	NR	NR	NR	NR	1	0
• Loss to Follow-up	3	3	2	0	NR	NR
• Other	9	1	6	2	4	0
Included in Primary Efficacy Analysis	534	266	271	135	112	57
Included in Safety Analysis	533	265	271	135	113	57

e) Limitations/Sources of Bias

Select quality characteristics are assessed and summarized in Table 5. SIGN-50 quality assessment is provided in Table 8.

All three trials were of high quality based on the SIGN-50 quality checklist for randomized control trials[97]. All studies were double blinded and used appropriate randomization methods and sample sizes were targeted for sufficient statistical power of primary outcomes. Details of blinding and randomisation methods are summarized in section 6.2.8.1a.

- Both RECOURSE and TERRA used ITT populations for their efficacy analyses. J003-10040030 used an efficacy population that excluded three patients from the ITT population.
- RECOURSE and TERRA limit ECOG PS to 0-1 limiting the applicability of the results to patients with higher ECOG PS and thus poorer performance status. The number of patients with ECOG PS of 2 in J003-10040030 are low (5/169), therefore, the results of the study are not necessarily representative of or generalizable to this ECOG performance status.
- All three studies were funded by the manufacturer of the drug of interest. The manufacturer in collaboration with the trial investigators designed the study, and collected and analyzed the data.
- Hematological adverse events (e.g. neutropenia, leukopenia, anemia, and thrombocytopenia) were more common in the treatment than placebo group and may have compromised blinding or introduced detection bias.

These adverse events resulted in more dose reductions and interruptions in the treatment group for all trials compared to the placebo group. PFS, TTF, and type and duration of response were independently assessed in J003-10040030. Trial data were reviewed and evaluated by an independent safety monitoring board in TERRA. An independent data monitoring committee and independent statistical analysis validation were employed in RECOURSE. These independent assessments help to limit the potential introduction of bias.

- Population race was majority white (58%) in RECOURSE, entirely Asian in TERRA, and Japanese in J003-10040030. The generalisability of trial outcomes to other races may be limited.
- Patient data censorship occurred in all trials for patients alive at time of primary efficacy analyses and for missing data. Missing OS, PFS, TTF, and duration of response data in TERRA was censored to last follow-up date. J003-10040030 censored missing data to last evaluation or last confirmable survival date. Patients who received non-study cancer treatment were censored to last tumor assessment prior to violation in RECOURSE. RECOURSE specified imputation occurred in cases where only the day was missing from partial death or clinical progression dates.
- Being refractory or intolerant to treatment was not explicitly defined in the J003-10040030 trial, however previous treatment was considered prior to enrolment to ensure patient eligibility.
- None of the trials included measures of health related quality of life, which was highlighted as an outcome of interest in the patient advocacy group surveys.
- Notably fewer patients in the TERRA trial received treatment with bevacizumab, cetuximab, and/or panitumumab prior to enrollment in the study compared to the other two trials. Panitumumab was not a prior treatment for any patients in J003-10040030.

Table 8: Sign-50 Quality Assessment

	RECOURSE[1]	TERRA[2]	J003-10040030[6]
Internal Validity			
1.1 Study addresses appropriate and clearly focused question	Yes	Yes	Yes
1.2 The assignment of subjects to treatment groups is randomized	Yes	Yes	Yes
1.3 An adequate concealment method is used	Yes	Yes	Yes
1.4 The design keeps subjects and investigators "blind" about treatment allocation	Yes	Yes	Yes
1.5 Treatment and control groups are	Yes	Yes	Yes

	RECOURSE[1]	TERRA[2]	J003-10040030[6]
Internal Validity			
similar at the start of the trial			
1.6 The only difference between groups is the treatment under investigation	Yes	Yes	Yes
1.7 All relevant outcomes are measured in a standard, valid and reliable way	Yes	Yes	Yes
1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	92.9%- Trifluridine-tipiracil 98.9%- Placebo	97.4%- Trifluridine-tipiracil 100%- Placebo	96.4%-Trifluridine-tipiracil 100%- Placebo
1.9 All the subjects are analyzed in the groups to which they were randomly allocated (intent to treat analysis)	Yes	Yes	No
1.10 Where the study is carried out at more than one site, results are comparable for all sites	Yes	Can't Say	Can't Say
Overall Assessment of the Study			
2.1 How well was the study done to minimize bias?	High Quality	High Quality	High Quality
2.2 Taking into account clinical considerations, your evaluation of the methodology used and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes	Yes	Yes
2.3 Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	Yes	Yes

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were based on ITT populations in RECOURSE and TERRA. J003-10040030 used a population excluding two untreated patients and one patient that had violated study protocol. The DCR and ORR analyses were completed using the TR population for each trial. Safety analyses were completed using the AT population in all trials. Missing efficacy data was censored to last confirmable survival date in TERRA and J003-10040030 and imputation for partial death or clinical progression dates occurred where only the day was missing for RECOURSE.

A summary of efficacy results can be found in Table 9 and a summary of safety results can be found in Tables 10 and 11.

Overall Survival

Overall survival was the primary endpoint of all trials, defined as the time between randomization and death due to any cause. All trials reported statistically significant improvements in OS in favour of trifluridine-tipiracil treatment.

In RECOURSE formal OS analysis occurred once 574 deaths were observed. Four deaths occurred on the date the 571st event occurred. January 24th, 2014 was the cut-off date for OS data analysis. Patients having documented survival status after this date had survival times censored to the cut-off date. By the cut-off date 68.9% of patients in the treatment arm had died and 79.9% of patients in the placebo arm had died. The median OS was 7.1 months in the trifluridine-tipiracil group and 5.3 in the placebo group. An absolute improvement in median OS of 1.8 months for treatment was reported (HR=0.68, 95%CI: 0.58-0.81, p<0.001). The median follow-up time for OS analysis was 11.8 months. OS was analyzed using a two-sided, stratified log-rank test, stratified Cox model and associated Kaplan-Meier survival estimates were used to determine the hazard ratio and 95% confidence intervals. The ITT population was used for this analysis (n=800)[1,10].

Updated RECOURSE OS was reported in a conference abstract. In addition to the 574 deaths of the primary analysis, 138 deaths occurred. By the updated cut-off date 86.7% of patients in the treatment arm had died and 93.6% of patients in the placebo arm had died. Median OS was 7.2 months in the trifluridine-tipiracil group and 5.2 months in the placebo group. An absolute improvement in median OS of 2.0 months in favor of the treatment group was reported (HR=0.69, 95%CI: 0.59-0.81, p<0.0001). Median follow-up time for the updated analysis was 19.1 months. The cut-off date for follow-up analysis was October 8th, 2014, 7.4 months following the original cut-off date of January 24th, 2014 stipulated in the RECOURSE protocol. The ITT population was used for this analysis (n=800)[9].

In TERRA formal OS analysis occurred once 288 deaths were observed. February 16th, 2016 was the cut-off date for OS analysis. Patients alive at the cut-off date or lacking confirmation of death had survival times censored to the cut-off date or last follow-up, whichever was earlier. By the cut-off date 75.6% of patients in the treatment arm had died and 82.2% of patients in the placebo arm had died. The median OS was 7.8 months in the trifluridine-tipiracil group and 7.1 months in the placebo group. An absolute improvement in median OS of 0.7 months for treatment was reported (HR=0.79, 95%CI: 0.62-0.99, p=0.035). Median follow-up time for OS analysis was 13.8 months and 13.4 months for the trifluridine-tipiracil and the placebo group respectively. The median follow-up time for OS analysis was 6.43 months for the trifluridine-tipiracil group and 5.08 months for the placebo group.

OS was analyzed using a two-sided, stratified log-rank test, stratified Cox model and associated Kaplan-Meier survival estimates were used to determine the hazard ratio and 95% confidence intervals. The ITT population was used for this analysis (n=406)[2].

In J003-10040030 OS analysis occurred once 121 deaths were observed. February 4th, 2011 was the cut-off date for OS analysis. Patients having documented survival status after this date had survival times censored to the cut-off date. By the cut-off date 67.0% of patients in the treatment arm had died and 84.2% of patients in the placebo arm had died. The median OS was 9.0 months in the trifluridine-tipiracil group and 6.6 months in the placebo group. An absolute improvement in median OS of 2.4 months for treatment was reported (HR=0.56, 95%CI: 0.39-0.81, p=0.0011). Median follow-up time for OS analysis was 11.3 months. OS was analyzed using a stratified log-rank test, stratified Cox model and associated Kaplan-Meier survival estimates were used to determine the hazard ratio and 80% and 95% confidence intervals. The full analysis set (FAS) population was used in this analysis (n=169)[6].

Progression-free Survival

All trials reported statistically significant improvements in PFS in favor of trifluridine-tipiracil treatment.

The median PFS in RECOURSE was 2.0 months for the trifluridine-tipiracil group compared to 1.7 months in the placebo group (HR=0.48, 95%CI: 0.41-0.57, p<0.001). In TERRA the median PFS was 2.0 months and 1.8 months for the trifluridine-tipiracil and placebo groups respectively (HR=0.43, 95%CI: 0.34-0.54, p<0.001). In J003-10040030 the median PFS was 2.0 and 1.0 months for the trifluridine-tipiracil and placebo groups respectively (HR=0.41, 95%CI: 0.28-0.59, p<0.0001).

Time to Treatment Failure

All trials reported statistically significant improvements in TTF in favor of trifluridine-tipiracil treatment.

The median TTF in RECOURSE was 1.9 months for the trifluridine-tipiracil group compared to 1.7 months in the placebo group (HR=0.50, 95%CI: 0.42-0.58, p<0.0001). In TERRA the median TTF was 1.9 months and 1.8 months for the trifluridine-tipiracil and placebo groups respectively (HR=0.46, 95%CI: 0.37-0.58, p<0.001). In J003-10040030 the median TTF was 1.9 and 1.0 months for the trifluridine-tipiracil and placebo groups respectively (HR=0.40, 95%CI: 0.28-0.56, p<0.0001).

Overall Response Rate

All trials reported statistically insignificant improvements in ORR in favor of trifluridine-tipiracil. ORR is based on pooled partial and complete tumor response. Details of ORR can be found in Table 9. The TR population was used for these analyses.

Proxies for Health Related Quality of Life

Direct measures of health related quality of life (QoL) were not reported in any of the included studies. However, two post hoc analyses intended to estimate effects of trifluridine-tipiracil treatment on QoL were completed on RECOURSE. Since the outcomes included in these analyses were proxies for QoL, the studies did not fit

the inclusion criteria and were not included in the systematic review. However, an overview of the results has been summarized here.

van Cutsem and colleagues investigated performance status through ECOG scores at treatment discontinuation and adverse events of high prevalence likely to affect QoL [98]. AEs included were nausea combined with vomiting, diarrhoea, dysgeusia, and fatigue or asthenia. Descriptive statistics were reported. Patients in the treatment arm were more likely to experience those AEs than patients in the placebo arm. The frequency of those AEs was greatest during cycle 1 in the treatment arm. Experience of at least one of those AEs in either arm was associated with a longer median duration of treatment. Hospitalizations resulted from some of the selected AEs in the trifluridine-tipiracil arm, vomiting (1.1%), nausea (0.6%), diarrhea (0.8%), and dehydration (0.6%)[10,98]. Study discontinuation resulting from the selected AEs occurred in 2.5% of patients in the treatment arm and 2.3% of patients in the placebo arm[10,98]. In terms of ECOG PS 65% of treatment patients and 60% of placebo patients with a baseline PS of 0 maintained that status at discontinuation. Improvement in PS status (1 to 0) occurred in 4% of the treatment arm and 3% of the placebo arm and maintenance of a PS of 1 from baseline to discontinuation occurred in 67% and 63% of treatment and placebo patients. Trifluridine-tipiracil significantly increased median time to PS of 2 or greater compared to placebo (5.7 vs 4.0 months; HR 0.66; 95%CI 0.56-0.78; $p<0.001$). Together these results suggest that trifluridine-tipiracil treatment did not result in a deterioration of patient QoL compared to placebo. Notably, PS at discontinuation is not a validated or formally recognized surrogate for QoL. AEs were limited to those expected to affect QoL, potentially excluding informative AE's.

Tabernero and colleagues conducted a quality-adjusted time without symptoms of disease or toxicity (QTWIST) analysis to assess quality adjusted survival time [85]. Duration of survival was partitioned into three discrete health states: toxicity, time without symptoms or toxicity before disease progression, and relapse. Toxicity was defined as time spent with selected grade 3 or 4 treatment related AEs before progression or censoring. The AEs selected were nausea, vomiting, diarrhea, fatigue or asthenia, anorexia, and febrile neutropenia. Relapse was defined as time between disease progression and death or censoring. Estimated mean durations for each health state were weighted by a utility coefficient and combined into the global QTWIST score. An assumed utility coefficient of 1 was used for the time without symptoms or toxicity before disease progression health state and 0.5 was used for both toxicity and relapse health states. Large variations in the coefficients assigned to relapse and time without symptoms or toxicity before disease progression resulted in minimum and maximum quality adjusted survival spanning 1.28 to 1.73 months. All health states were longer for trifluridine-tipiracil patients compared to placebo. A QTWIST score of 5.48 months was found for the treatment arm and 3.98 months for the placebo arm giving a 1.5 month difference in favor of treatment (95%CI 1.49-1.52). As utility coefficients were not directly elicited from patients hypothetical thresholds were defined. This limitation is countered by the limited sensitivity the analysis had to the coefficient used. AEs were limited to those expected to affect QoL and those of grade 3 or 4 potentially excluding informative data on adverse event impact on quality of life. This is of particular note for lower graded AEs of long duration.

Disease Control Rate

All trials reported statistically significant improvements in DCR in favor of trifluridine-tipiracil treatment.

In RECOURSE 44.0% of patients in the trifluridine-tipiracil group and 16.3% of patients in the placebo group experienced complete or partial response or disease stability (p<0.0001). In TERRA 44.1% of patients in the trifluridine-tipiracil group and 14.6% of patients in the placebo group experienced complete or partial response or disease stability (p<0.0001). In J003-10040030 43% of patients in the trifluridine-tipiracil group and 11% of patients in the placebo group experienced complete or partial response or stability of disease (p<0.0001).

Metastatic Resection Rate

Metastatic resection rates were not captured in the study data for TERRA and J003-10040030. Three patients in RECOURSE underwent resection for metastases during the study, which violated study protocol[10].

Subgroup Analysis of Efficacy Outcomes[7]

Patients that received previous pelvic radiation therapy were identified as a subgroup of interest for this review. This therapy has a frequent side effect of myelosuppression and could potentially impact the safety of trifluridine – tipiracil, which has higher rates of hematological AEs such as neutropenia. For all three trials a small sample size of this subgroup makes it difficult to determine any safety trends. The OS and PFS and safety outcomes for this subgroup is intended for descriptive purposes only.

In RECOURSE 24 (3%) patients received previous pelvic radiation therapy (20 in the trifluridine-tipiracil group and 4 in the placebo group). The median OS was 7.8 months in the trifluridine-tipiracil group and 3.4 in the placebo group (HR=0.64, 95%CI: 0.15-2.71). The median PFS was 3.6 months for the trifluridine-tipiracil group compared to 1.6 months in the placebo group (HR=0.39, 95%CI: 0.09-1.69).

In TERRA 24 (5.9%) patients received previous pelvic radiation therapy (19 in the trifluridine-tipiracil group and 5 in the placebo group). The median OS was 8.4 months in the trifluridine-tipiracil group and 7.9 in the placebo group (HR=0.72, 95%CI: 0.26-2.04). The median PFS was 3.5 months for the trifluridine-tipiracil group compared to 1.9 months in the placebo group (HR=0.37, 95%CI: 0.11-1.25).

In J003-10040030 9 (10.7%) patients received previous pelvic radiation therapy (6 in the trifluridine-tipiracil group and 3 in the placebo group). The median OS was 7.8 months in the trifluridine-tipiracil group and 6.0 in the placebo group (HR=0.57, 95%CI: 0.10-3.18). The median PFS was 1.4 months for the trifluridine-tipiracil group compared to 1.0 months in the placebo group (HR=0.63, 95%CI: 0.10-3.82).

The incidence of the most frequent AEs appear to be similar to the overall population in all trials. In RECOURSE AEs pertaining to blood and lymphatic system disorders occurred in 18 (90%) patients in the treatment arm and 1 (25%) patient in the placebo arm. In TERRA they occurred in 11 (57.9%) patients in the treatment arm and 1 (20%) patient in the placebo arm. In J003-10040030 they occurred in 1 (10%) patients in the treatment arm and 0 patients in the placebo arm[10].

Table 9: Summary of efficacy outcomes in included trials

	RECOURSE[1,10]		RECOURSE[9]*		TERRA[2]		J003-10040030[6,10]	
	Trifluridine-tipiracil (n=534)	Placebo (n=266)	Trifluridine-tipiracil (n=534)	Placebo (n=266)	Trifluridine-tipiracil (n=271)	Placebo (n=135)	Trifluridine-tipiracil (n=112)	Placebo (n=57)
Overall Survival (Months)								
Median (95% CI)	7.1 (6.5-7.8)	5.3 (4.6-6.0)	7.2 (6.6-7.8)	5.2 (4.6-5.9)	7.8 (7.1-8.8)	7.1 (5.9-8.2)	9.0 (7.3-11.3)	6.6 (4.9-8.0)
Hazard Ratio (95% CI)	0.68 (0.58-0.81)		0.69 (0.59-0.81)		0.79 (0.62-0.99)		0.56 (0.39-0.81)	
p-value	<0.001		<0.0001		0.035		0.0011	
Median Follow-up	6.43	5.08	NR		13.8	13.4	11.3	
Progression Free Survival (Months)								
Median (95% CI)	2.0 (1.9-2.1)	1.7 (1.7-1.8)	2.0 (1.9-2.1)	1.7 (1.7-1.8)	2.0 (1.9-2.8)	1.8 (1.7-1.8)	2.0 (1.9-2.8)	1.0 (1.0-1.0)
Hazard Ratio (95% CI)	0.48 (0.41-0.57)		0.49 (0.42-0.58)		0.43 (0.34-0.54)		0.41 (0.28-0.59)	
p-value	<0.001		<0.0001		<0.001		<0.0001	
Time to Treatment Failure (Months)								
Median (95% CI)	1.9 (1.9-2.0)	1.7 (1.7-1.8)	NR		1.9 (1.9-2.2)	1.8 (1.7-1.8)	1.9 (1.3-2.1)	1.0 (1.0-1.0)
Hazard Ratio (95% CI)	0.50 (0.42-0.58)		NR		0.46 (0.37-0.58)		0.40 (0.28-0.56)	
p-value	<0.0001		NR		<0.001		<0.0001	
Overall Response Rate								
n	502	258	NR		261	130	112	55
Complete, partial n (%)	8 (1.6)	1 (0.4)	NR		3 (1.1)	0	1 (1)	0
p-value	0.2862		NR		0.554		1.000	
Disease Control Rate								
Complete, partial, stable disease n (%)	221 (44.0)	42 (16.3)	NR		115 (44.1)	19 (14.6)	48 (43)	6 (11)
p-value	<0.0001		NR		<0.0001		<0.0001	

**Conference Abstract*

NR-Not Reported

Harms Outcomes

All three trials provided data on harm outcomes, although data provided by J003-10040030 was limited. Harms data is summarized in Table 10. Further detail pertaining to grade 3 or greater events is summarized in Table 11; number of events is presented for treatment and placebo arms.

In all trials the main adverse events that differed between treatment groups (>10% difference) were neutropenia, leukopenia, and anemia. Vomiting had a greater than 10% difference between groups in the J003-10040030 trial.

In the RECOURSE trial, grade 3 or greater adverse events occurred in 69% of patients in the treatment arm and 52% of the patient in the placebo arm[1]. The incidence of the following adverse events was higher in patients treated with trifluridine-tipiracil when compared to those in the placebo arm: neutropenia (38% vs 0%), leukopenia (21% vs 0%), anemia (18% vs 3%), thrombocytopenia (5% vs <1%), febrile neutropenia (4% vs 0%), diarrhea (3% vs <1%), hyperglycemia (2% vs 0%), and hand-foot syndrome (2% vs 0%). The grade 3 or higher incidence of anorexia (decreased appetite) was 3.6% in the trifluridine-tipiracil and 4.9% in the placebo groups, there was no reported incidence of grade 3 or higher bone marrow failure or liver injury[10]. The incidence of following grade 3 or greater adverse events was higher in the treatment group, but by a difference of 1% or less: nausea, vomiting, stomatitis, small intestinal obstruction, pneumonia, hypocalcemia, and hypokalemia. Incidence of SAEs was at 29.6% in the trifluridine-tipiracil group and 33.6% in the placebo group. 10.3% of patients in the trifluridine-tipiracil group discontinued treatment due to an AE compared to 13.6% of patients in the placebo group. One (0.2%) treatment-related death in the trifluridine-tipiracil arm was reported resulting from septic shock.

In the TERRA trial, grade 3 or greater AEs occurred in 45.8% of patients in the treatment arm and 10.4% in the placebo arm[2]. The incidence of the following adverse events was higher in patients treated with trifluridine-tipiracil when compared to those in the placebo arm: neutropenia (33.2% vs 0%), leukopenia (20.7% vs 0%), anemia (17.7% vs 5.9%), fatigue (6.7% vs 0%), vomiting (3.7% vs 0%), small intestinal obstruction (1.1% vs 0%), thrombocytopenia (3% vs 1.5%), increased creatinine (1.1% vs 0%), bone marrow failure (1.1% vs 0%), and hypoalbuminemia (3% vs 0%). The incidence of following grade 3 or greater adverse events was higher in the treatment group, but by a difference of 1% or less: decreased appetite, nausea, diarrhea, asthenia, palpitations, abdominal discomfort, stomatitis, upper respiratory tract infection, hypertension, hepatic function abnormal, syncope, increase alkaline phosphatase, hyperglycemia, hypocalcemia and hyperkalemia. Incidence of drug related SAEs was at 23.2% and 23% in the trifluridine-tipiracil and placebo groups respectively. AEs led to discontinuation of treatment in 10% and 9.6% of patients in the trifluridine-tipiracil and placebo groups respectively. AEs that led to death occurred in five patients (1.8%) in the trifluridine-tipiracil arm and one patient (0.7%) in the placebo arm. These deaths resulted from small intestinal obstruction, hepatic failure, pneumonia, acute kidney failure, and unknown cause in the treatment group and from decreased appetite in the placebo group. No treatment-related deaths occurred.

In J003-10040030 grade three or greater adverse events occurred in 69% of patients in the treatment arm and 16% of patients in the placebo arm. This trial reported that the incidence of the following adverse events was higher in patients treated with trifluridine-tipiracil when compared to those in the placebo arm: neutropenia (50% vs 0%), vomiting (34% vs 0%), leukopenia (28% vs 0%), anemia (17% vs 5%), diarrhea (6% vs 0%), febrile neutropenia (4% vs 0%), nausea (4% vs 0%) and fatigue (6% vs 4%). SAEs occurred in 19% of the patients treated with trifluridine-tipiracil and 9% of patients in the placebo group. 4% of patients receiving trifluridine-tipiracil discontinued treatment due to drug-related

adverse events. In the placebo group 2% of patients discontinued the study due to drug-related adverse events. No treatment-related deaths occurred in J003-10040030[6].

Table 10: Summary of Adverse Event Related Harms

	RECOURSE[1,10]		TERRA[2,10]		J003-10040030[6,10]	
Adverse Events, n (%)	Treatment (n=533)	Placebo (n=265)	Treatment (n=271)	Placebo (n=135)	Treatment (n=113)	Placebo (n=57)
Adverse Events Any Grade	524 (98)	247 (93)	244 (90)	70 (52)	111 (98)	52 (91)
Adverse Events ≥Grade 3	370 (69)	137 (52)	124 (46)	14 (10)	78 (69)	9 (16)
Serious Adverse Events	158 (30)	89 (34)	63 (23)	31 (23)	21 (19)	5 (9)
Withdrawal Due to Adverse Event	21 (4)	5 (2)	27 (10)	13 (9.6)	5 (5)	1 (2)
Adverse Event Related Death	17 (3.2)	30 (11.3)	5 (1.8)	1 (0.7)	1(0.9)	0
Treatment-Related Death	1 (0.2)	0	0	0	0	0

NR-Not reported

Table 11: Adverse events greater or equal to Grade 3

	RECOURSE[1,10]		TERRA[2,10]		J003-10040030[6,10]	
Adverse Events, n (%)	Treatment (n=533*)	Placebo (n=265*)	Treatment (n=271)	Placebo (n=135)	Treatment (n=113)	Placebo (n=57)
Any Adverse Event	370 (69)	137 (52)	124 (45.8)	14 (10.4)	78 (69)	9 (16)
Nausea	10 (2)	3 (1)	2 (0.7)	0	5 (4)	0
Decreased Appetite	19 (4)	13 (5)	2 (0.7)	0	5 (4)	2 (4)
Fatigue	21 (4)	15 (6)	9 (6.7)	0	7 (6)	2 (4)
Vomiting	11 (2)	1(<1)	5 (3.7)	0	38 (34)	0
Diarrhea	16 (3)	1 (<1)	3 (2.2)	1 (0.7)	7 (6)	0
Anorexia	(3.6)	(4.9)	81 (29.9)	22 (16.3)	5 (4)	2 (4)
Asthenia	18 (3)	8 (3)	2 (0.7)	0	NR	NR
Palpitations	0	0	1 (0.4)	0	NR	NR
Bone marrow failure	0	0	3 (1.1)	0	NR	NR
Abdominal discomfort	0	0	1 (0.4)	0	NR	NR
Stomatitis	2 (<1)	0	1 (0.4)	0	0	0
Dyspnea	14 (3)	10 (4)	0	1 (0.7)	2 (2)	0
Small intestinal obstruction	6 (1)	1 (<1)	3 (1.1)	0	2 (2)	0
Upper respiratory tract infection	0	0	1 (0.4)	0	0	0
Hypertension	8 (2)	10 (4)	1 (0.4)	0	0	0

	RECOURSE[1,10]		TERRA[2,10]		J003-10040030[6,10]	
Adverse Events, n (%)	Treatment (n=533*)	Placebo (n=265*)	Treatment (n=271)	Placebo (n=135)	Treatment (n=113)	Placebo (n=57)
Liver injury	0	0	0	1 (0.7)	NR	NR
Edema peripheral	1 (<1)	2 (1)	0	1 (0.7)	1 (1)	1 (2)
Pneumonia	4 (1)	1 (<1)	0	1 (0.7)	3 (3)	0
Hepatic function abnormal	0	0	1 (0.4)	0	NR	NR
Syncope	0	0	1 (0.4)	0	NR	NR
Febrile neutropenia	20 (4)	0	0	0	5 (4)	0
Hand-foot syndrome	12 (2)	0	1 (0.4)	0	0	0
Cardiac ischemia	1 (<1)	1 (<1)	1 (0.4)	0	1 (1)	0
Neutropenia	200/528 (38)	0	90 (33.2)	0	57 (50)	0
Leukopenia	113/528 (21)	0	56 (20.7)	0	32 (28)	0
Anemia	96/528 (18)	8/263 (3)	48 (17.7)	8 (5.9)	19 (17)	3 (5)
Thrombytopenia	27/528 (5)	1/263 (<1)	8 (3.0)	2 (1.5)	5 (4)	2 (4)
Increased alanine aminotransferase	10/526 (2)	10/263 (4)	3 (1.1)	4 (3.0)	0	0
Increased aspartate aminotransferase	23/524 (4)	16/262 (6)	10 (3.7)	7 (5.2)	2 (2)	0
Increased bilirubin	45/526 (9)	31/262 (12)	19 (7)	10 (7.4)	3 (3)(	1 (2)
Increase alkaline phosphatase	24/526 (8)	28/262 (11)	11 (4.1)	5 (3.7)	3 (3)	1 (2)
Increase creatinine	5/527 (<1)	2/263 (<1)	3 (1.1)	0	0	1 (2)
Hyperglycemia	8 (2)	0	7 (2.6)	3 (2.2)	NR	NR
Hypoalbuminemia	4 (1)	2 (1)	8 (3)	0	NR	NR
Hyponatremia	7 (1)	4 (2)	12 (4.4)	6 (4.4)	NR	NR
Hypocalcemia	1 (<1)	0	3 (1.1)	1 (0.7)	NR	NR
Hypokalemia	12 (2)	2 (1)	2 (0.7)	11 (8.1)	NR	NR
Hyperkalemia	1 (<1)	2 (1)	1 (0.4)	0	NR	NR
Hypercalcemia	0	1 (<1)	0	1 (0.7)	NR	NR

NR-Not Reported

* -n for laboratory abnormalities includes only patients with at least one post-baseline measurement (displayed as denominator in table values)

6.4 Ongoing Trials

No ongoing clinical trials investigating trifluridine-tipiracil efficacy in patients with refractory mCRC met the eligibility criteria of this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified as relevant to the pCODR review of the efficacy and safety of trifluridine-tipiracil (Lonsurf) in patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti VEGF therapy, and if KRAS wild-type, anti EGFR therapy. Topics in this section are provided as supporting information and were not systematically reviewed.

7.1 Critical appraisal of the findings of a systematic review and network meta-analysis comparing the efficacy and safety of trifluridine-tipiracil to regorafenib[56].

7.1.1 Objective

This critical appraisal was completed due to the inclusion of regorafenib as a comparator of interest in the review protocol and because no RCTs comparing trifluridine-tipiracil to regorafenib were found. The consulted provinces, registered clinicians, patient groups, and the submitter also highlighted regorafenib as an important comparator. Of note, regorafenib is not currently publically funded in any provinces.

7.1.2 Findings

Retrospective studies showing comparable efficacy, but differing toxicity profiles between trifluridine-tipiracil and regorafenib prompted further investigation. Abrahao and colleagues undertook a systematic review and network meta-analysis to compare the two treatment options given a lack of direct comparisons via a head-to-head RCT.

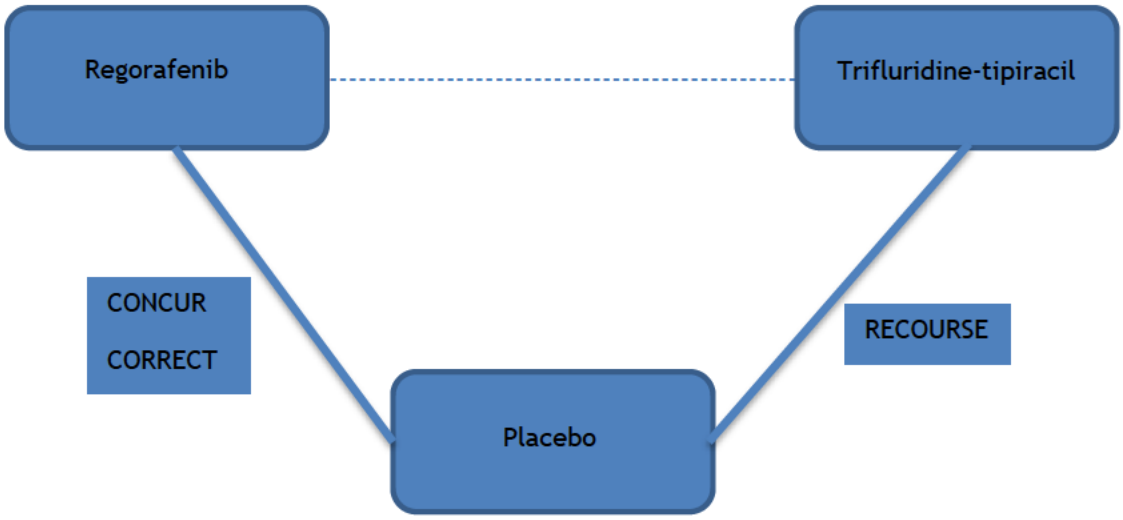
Methodology

The systematic review used the criteria summarized in Table 12 to identify eligible studies from PubMed, Medline, Embase, Scopus, and Cochrane databases. Databases were searched from inception until November of 2015. If multiple publications were available for the same trial, only the most recent was included. A graphical representation of the evidence network can be found in Figure 2.

Table 12: Systematic Review Inclusion Criteria[56]

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished phase III trials reported in English	Adult patients (≥18 years) with refractory mCRC	Trifluridine-Tipiracil (Lonsurf) Or Regorafenib	• BSC • placebo	Primary • OS Secondary • PFS • ORR • DCR • Toxicity/Safety
[Abbreviations] **BSC** - best supportive care; **DCR** - disease control rate; **mCRC** - metastatic colorectal cancer; **ORR** - objective tumour response rate; **OS** - overall survival; **PFS** - progression-free survival				

Figure 2: Indirect treatment comparison network[56]



Data for the selected outcomes of interest were extracted from included studies. Toxicity and safety included all AEs of all grades. Subgroup analyses on hematologic toxicity and non-hematologic toxicities (hand-foot skin reaction, fatigue, and diarrhoea) were performed. Variance estimates on HRs were calculated using the reported CIs. Pooled effect for the endpoints OS and PFS was measured using HRs with 95% CIs in random-effects models. Pooled effect for all other outcomes was evaluated using risk difference in random-effects models. Review Manager 5.1 software was used to pool the data for the pairwise direct meta-analysis. For the indirect comparison network meta-analyses were performed. Study quality was assessed via the Cochrane risk of bias tool. It is unclear whether any of the review was completed in duplicate.

Results

The literature search resulted in 914 citations. Of these, 422 were excluded based on abstract review and 19 were excluded due to language of publication being non-English. The remaining 473 abstracts were reviewed resulting in 14 exclusions due to trial type, two due to patient group, and 454 due to article type (e.g. reviews, case reports, and editorials). A total of three trials were included in the review involving 1764 patients. The trials included were CORRECT, CONCUR, and RECOURSE. All trials were centrally randomized and double blinded. All used an ITT population for primary efficacy analyses. Secondary endpoints of PFS, safety, ORR and DCR were reported in all trials. RECOURSE was the only trial that did not report quality of life.

Trial characteristics

All studies included an adult patient population diagnosed with mCRC previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti VEGF therapy, and if KRAS wild-type, anti EGFR therapy. The trials were superiority trials comparing the therapy of interest with placebo. Dosage in CORRECT and CONCUR was 160mg of regorafenib or matched placebo once daily on days 1-21 of each 28 day cycle. In RECOURSE, trifluridine-tipiracil or placebo were administered at 35mg/m^2 twice daily on days 1-5 and 8-12 of a 28 day cycle. A total of 641 patients received regorafenib, 534 received trifluridine-tipiracil, and 589 received placebo. Most demographic characteristics were similar between the included trials and are summarized in Table 13. The majority of patients in CONCUR had an ECOG status of 1 whereas the majority of patients in RECOURSE and CORRECT had an ECOG status of 0.

Table 13: Systematic Review Inclusion Criteria[56]

	RECOURSE		CONCUR		CORRECT	
	Trifluridine-tipiracil	Placebo	Regorafenib	Placebo	Regorafenib	Placebo
N randomized	534	266	136	68	505	255
Age (yrs)						
Median	63	63	57	55.5	61	61
Sex (%)						
Male	61	62	63	49	62	60
Female	39	38	38	51	38	40
ECOG performance Status (%)						
0	56	55	26	22	52	57
1	44	45	74	78	48	43

Alpha values were not reported for any analyses. p values were not reported for the OS or PFS direct comparisons, nor for the indirect subgroup safety comparisons. Where available they are incorporated into this critical appraisal.

Efficacy

Since 91 therapy patients and 53 placebo patients received prior study treatment with regorafenib in RECOURSE, a subgroup excluding those patients (433 therapy and 213 placebo patients) was used in the OS and PFS meta-analysis. Trifluridine-tipiracil was not a prior treatment for any patients in the other two trials.

For the direct meta-analysis regorafenib showed an OS benefit compared to placebo (HR=0.67; 95%CI: 0.48-0.93) as did trifluridine-tipiracil compared to placebo (HR=0.69; 95%CI: 0.57-0.83). The same benefit holds for PFS analysis in the direct pairwise meta-analysis for both regorafenib (HR=0.40; 95%CI: 0.26-0.63) and trifluridine-tipiracil (HR=0.47; 95%CI: 0.39-0.56) compared to placebo.

The indirect comparison showed both treatments to have comparable effect on OS (HR=0.96; 95%CI: 0.57-1.66, p=0.91) and PFS (HR=0.85; 95%CI: 0.40-1.81, p=0.67). No significant difference between regorafenib and trifluridine-tipiracil was found in the indirect comparison for ORR (RD=0.0061; 95%CI: -0.044-0.056, p=0.81) or DCR (RD=0.091; 95%CI: -0.20-0.386, p=0.54).

Safety

AT populations were used for safety analyses in all trials. This excluded five patients with missing toxicity profiles from CORRECT and two patients from RECOURSE. Patients in RECOURSE that had received prior treatment with regorafenib were also excluded from analyses. Indirect comparison showed regorafenib treatment to have higher all-grade any toxicity than trifluridine-tipiracil (RD=0.35; 95%CI: 0.04-0.67, p=0.013). This difference held true for all grade 3-5 toxicity (RD=0.22; 95%CI: 0.13-0.31, p<0.001).

Lower all-grade hematological toxicity for regorafenib was found through the subgroup analysis. That analysis encompassed anemia (RD=-0.38; 95%CI: -0.45- -0.30), neutropenia (RD=-0.60; 95%CI: -0.66- -0.55),

and thrombocytopenia (RD=-0.23; 95%CI: -0.31- -0.15). This trend held in grade 3-5 hematologic toxicity for anemia (RD=-0.12; 95%CI: -0.17- -0.09) and neutropenia (RD=-0.35; 95%CI: -0.40- -0.30).

Regorafenib was associated with higher all-grade hand-foot skin reaction (RD=0.58; 95%CI: 0.36-0.81). Grade 3-5 hand-foot skin reaction (RD=0.16; 95%CI: 0.13-0.19). It was also associated with higher grade 3-5 fatigue (RD=0.04; 95%CI: 0.001-0.05).

No difference in grade 3-5 thrombocytopenia between the two treatments was found (RD=-0.02; 95%CI: -0.05-0.03), nor in grade 3-5 diarrhoea (RD=0.002; 95%CI: -0.11-0.12). All-grade fatigue (RD=0.13; 95%CI: -0.10-0.37) and diarrhoea (RD=0.23; 95%CI: -0.08-0.49) also showed no difference between treatments.

Critical Appraisal

The Methods team assessed the quality of the evidence network meta-analysis according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons. Details of the appraisal are presented in Table 14.

Table 14: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis

ISPOR Questions	Details and Comments
1. Is the population relevant?	Yes. Study demographics were similar between studies. RECOURSE included some patients with prior regorafenib treatment; however, those patients were excluded from analysis. ECOG status was higher in CONCUR compared to the other two studies.
2. Are any critical interventions missing?	No.
3. Are any relevant outcomes missing?	Yes. Health Related Quality of Life was not assessed.
4. Is the context applicable to your population?	Yes.
5. Did the researcher's attempt to identify and include all relevant randomized controlled trials?	Yes. A summary of the literature review was provided. However, it is unclear if screening calibration or duplicate data extraction occurred.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes.
7. Is it apparent that poor quality studies were included thereby leading to bias?	No. Study quality was listed as a selection criteria and was assessed using the Cochrane risk of bias tool. However, quality threshold for inclusion wasn't reported.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	No. Major primary and secondary outcomes were assessed by all studies except for quality of life.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Unclear. Patient characteristic differences were summarized qualitatively, however no tests for difference were conducted. A subgroup analysis of RECOURSE excluding patients with prior regorafenib treatment was conducted.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study result?	Unclear. RECOURSE patients with prior regorafenib treatment were excluded from comparison.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. Network meta-analyses methods (R package "netmeta") was used to preserve within-trial randomization.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable.

ISPOR Questions	Details and Comments
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize the bias with the analysis?	No. Effect modifiers were not discussed.
15. Was a valid rationale provided for the use of random-effects or fixed-effects model?	No. Random-effects models were used in analyses, however rationale for their use was not specified.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Unclear. Heterogeneity assumptions were not discussed.
17. If there are indications of heterogeneity, were subgroup analyses or-meta-regression analysis with pre-specified covariates performed?	Yes, in part. Heterogeneity was not addressed; however, subgroup analyses of safety data were undertaken. No meta-regression analysis was reported.
18. Is a graphical or tabular representation of the evidence network provided with information on the number or RCTs per direct comparison?	Yes. Refer to Figure 2.
19. Are the individual study results reported?	Yes. Individual study demographics and baseline characteristics were provided.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Yes.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. Hazard ratios and 95%CIs were reported for all outcomes.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No. However given the small network, ranks and probabilities would not be meaningful.
23. Is the impact of important patient characteristics on treatment effects reported?	No.
24. Are the conclusions fair and balanced?	Yes. The efficacy of both treatments were similar and the safety profiles differed, particularly for certain subsets of adverse events. Neither sequence of treatment nor superiority are suggested for either drug given the provided evidence.
25. Were there any potential conflicts of interest?	No. The authors reported there were no conflicts of interest. Details, such as funding source, were not reported.
26. If yes, were steps taken to address these?	Not applicable.

Summary

Conclusion

The pCODR methods team completed a critical appraisal of the findings from a systematic review and network meta-analysis comparing treatment efficacy and safety between trifluridine-tipiracil and regorafenib. The results of the comparison indicated that treatment with either drug resulted in similar OS, PFS, ORR, and DCR outcomes. Safety outcomes were the main difference between treatment options. Overall, regorafenib had greater all-grade and grade 3-5 AE incidence. Subgroup analyses indicated a difference in toxicity profile between treatments. The results were presented as potentially informative to clinical practice given individual patient histories. Treatment sequence and superiority were not determined.

The conclusions of the study are limited by some heterogeneity between the compared studies in patient characteristics and the fact that it is an indirect as opposed to direct comparison between drugs.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on trifluridine-tipiracil (Lonsurf) for metastatic colorectal cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Gastrointestinal Clinical Guidance Panel is comprised of three oncologists.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (November 2016) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were trifluridine-tipiracil, Lonsurf.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents and by publication year, studies published prior to 2012 were filtered out.

The search is considered up to date as of April 5th, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials May 2017, Embase 1974 to 2017 June 21, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Line #	Search	Results
1	(Lonsurf* or "Tipiracil / Trifluridine" or Tipiracil-Trifluridine or TAS 102 or TAS102 or Viroptic mixture with 5-CIMU or JNJ02 or 733030-01-8).ti,ab,ot,kf,kw,hw,rn,nm.	506
2	(Tipiracil* or 5-CIMU or MA 1 or MA1 or TPI or NGO10K751P or tas 1-462 or tas1462).ti,ab,ot,kf,kw,hw,rn,nm.	5774
3	Trifluridine/	2186
4	(Trifluridin* or "BRN 0568095" or BRN0568095 or CCRIS 2348 or CCRIS2348 or F3DThd or F3T or HSDB 8126 or HSDB8126 or NSC 529182 or NSC529182 or NSC 75520 or NSC75520 or Trifluoromethyldeoxyuridine or TFDU or Trifluorothymidine or RMW9V5RW38 or Viroptic or aflomin or bephen or ocufridine or tft or thriherpine or triflumann or trifluor thymidine or trifluoro	5005

	thymidine or trifluorodeoxythymidine or trifuridine or triherpin or triherpine or viromidin or virophta).ti,ab,ot,kf,kw,hw,rn,nm.	
5	3 or 4	5005
6	2 and 5	485
7	1 or 6	640
8	7 use medall	167
9	7 use cctr	63
10	*tipiracil plus trifluridine/ or (Lonsurf* or "Tipiracil / Trifluridine" or Tipiracil-Trifluridine or TAS 102 or TAS102 or Viroptic mixture with 5-CIMU or JNJ02).ti,ab,kw.	494
11	*Tipiracil/	9
12	(Tipiracil* or 5-CIMU or MA 1 or MA1 or TPI or tas 1-462 or tas1462).ti,ab,kw.	5355
13	11 or 12	5356
14	*Trifluridine/	1066
15	(Trifluridin* or "BRN 0568095" or BRN0568095 or CCRIS 2348 or CCRIS2348 or F3DThd or F3T or HSDB 8126 or HSDB8126 or NSC 529182 or NSC529182 or NSC 75520 or NSC75520 or Trifluoromethyldeoxyuridine or Trifluorothymidine or Viroptic or aflomin or bephen or ocufridine or tft or thriherpine or triflumann or trifluor thymidine or trifluoro thymidine or trifluorodeoxythymidine or trifuridine or triherpin or triherpine or viromidin or virophta).ti,ab,kw.	3172
16	14 or 15	3697
17	13 and 16	340
18	10 or 17	540
19	18 use oemezd	319
20	19 and conference abstract.pt.	144
21	limit 20 to yr="2012 -Current"	140
22	limit 21 to english language	140
23	19 not 20	175
24	8 or 9 or 23	405
25	limit 24 to english language	374
26	remove duplicates from 25	206
27	22 or 26	346

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#7	Search **#5 AND #6**	6
#6	Search **publisher[sb]**	533165
#5	Search **#1 OR #4**	146
#4	Search **#2 AND #3**	86
#3	Search **Trifluridin*[tiab] OR BRN 0568095[tiab] OR BRN0568095[tiab] OR CCRIS 2348[tiab] OR CCRIS2348[tiab] OR F3DThd[tiab] OR F3T[tiab] OR HSDB 8126[tiab] OR HSDB8126[tiab] OR NSC 529182[tiab] OR NSC529182[tiab] OR NSC 75520[tiab] OR NSC75520[tiab] OR Trifluoromethyldeoxyuridine[tiab] OR Trifluorothymidine[tiab] OR RMW9V5RW38[tiab] OR Viroptic[tiab] OR aflomin[tiab] OR bephen[tiab] OR ocufridine[tiab] OR tft[tiab] OR thriherpine[tiab] OR triflumann[tiab] OR trifluor thymidine[tiab] OR trifluoro thymidine[tiab] OR trifluorodeoxythymidine[tiab] OR trifuridine[tiab] OR triherpin[tiab] OR triherpine[tiab] OR viromidin[tiab] OR virophta[tiab] or TFDU[tiab]**	1314
#2	Search **Tipiracil*[tiab] OR 5-CIMU[tiab] OR MA 1[tiab] OR MA1[tiab] OR TPI[tiab] OR NGO10K751P[tiab]**	2317
#1	Search **"trifluridine tipiracil" [Supplementary Concept] OR Lonsurf[tiab]* OR "Tipiracil / Trifluridine"[tiab] OR Tipiracil-Trifluridine[tiab] OR TAS 102[tiab] OR TAS102[tiab] OR Viroptic mixture with 5-CIMU[tiab] OR JNJ02[tiab] OR 733030-01-8[rn]**	129

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: trifluridine/tipiracil, Lonsurf

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: trifluridine/tipiracil, Lonsurf

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

ESMO
http://oncologypro.esmo.org/Meeting-Resources

Search: trifluridine/tipiracil, Lonsurf, metastatic colorectal cancer –last 5 years

Study Selection

Two members of the pCODR Methods Team independently selected studies for inclusion in the review according to the predetermined protocol, all studies identified by either reviewer were included in full text review. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

REFERENCES

1. Mayer RJ, Van CE, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med [Internet]. 2015 May 14 [cited 2018 Jan 15];372(20):1909-19. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1414325

2. Xu J, Kim TW, Shen L, Sriuranpong V, Pan H, Xu R, et al. Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients With Previously Treated Metastatic Colorectal Cancer: The TERRA Study. J Clin Oncol. 2017 Dec 7;JCO2017743245.

3. Falcone A, Laurent S, Gravalos C, Benavides M, Longo MF, Ychou M, et al. Phase 3 RECOURSE trial of TAS-102 versus placebo with best supportive care in patients with metastatic colorectal cancer: European subgroup. Ann Oncol. 2015;Conference:(var.pagings). 26 ()(pp iv84), 2015. Date of Publication: June 2015.):iv84.

4. Sriuranpong V, Kim TW, Shen L, Xu J, Pan H, Xu R, et al. Phase III study of trifluridine/tipiracil versus placebo in Asian patients with metastatic colorectal cancer (TERRA study): Country subgroup. Ann Oncol. 2017;Conference:(Supplement 10):x42.

5. Falcone A, Garcia-Carbonero R, Tabernero J, Sobrero A, Peeters M, Zaniboni A, et al. Low rates of hospitalizations with TAS-102 in the European (EU) subregion of the Phase 3 RECOURSE trial in patients (pts) with metastatic colorectal cancer (mCRC). Eur J Cancer. 2015;51 Suppl 3:S383.

6. Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 2012 Oct;13(10):993-1001.

7. Falcone A, Ohtsu A, Van CE, Mayer R, Buscaglia M, Bendell JC, et al. Integrated safety summary (ISS) for trifluridine/tipiracil (TAS-102). Ann Oncol. 2016 Oct 11;27(Supplement 6):555P.

8. Folprecht G, Hofheinz R, Karthaus M, Moehler M, Jager E, Block A, et al. Time to grade >=3 adverse events in pts receiving trifluridine/ tipiracil (TAS-102). Oncology research and treatment. 2017;40(Supplement 3):168-70.

9. Mayer RJ, Ohtsu A, Yoshino T, Falcone A, Garcia-Carbonero R, Tabernero J, et al. TAS-102 versus placebo plus best supportive care in patients with metastatic colorectal cancer refractory to standard therapies: Final survival results of the phase III RECOURSE trial. J Clin Oncol [Internet]. 2016 [cited 2018 Jan 15];34(4 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/jco.2016.34.4_suppl.634

10. pan-Canadian Oncology Drug Review manufacturer submission: trifluridine and tipiracil - Lonsurf -35 mg/m2 to 80 mg tablets. Company: Taiho Oncology Inc. Princeton (NJ): Taiho Oncology Inc; 2017 Nov 6.

11. Hochster H, Hager S, Pipas JM, Tebbutt N, Laurent S, Gravalos C, et al. KRAS and BRAF gene subgroup analysis in the Phase 3 RECOURSE trial of TAS-102 versus placebo in patients with metastatic colorectal cancer. Ann Oncol. 2015 Jun;26(Supplement 4):iv111.

12. Nishina T, Yoshino T, Mizunuma N, Yamazaki K, Komatsu Y, Baba H, et al. Therapeutic effect of TAS-102 (A) in patients (pts) with metastatic colorectal cancer (mCRC) refractory to standard chemotherapy by the Kohne model (Km) [abstract]. J Clin Oncol [Internet]. 2012 [cited 2018 Jan 15];30(4 Suppl 1). Available from: http://ascopubs.org/doi/abs/10.1200/jco.2012.30.4_suppl.650

13. Longo-Munoz F, Argiles G, Tabernero J, Cervantes A, Gravalos C, Pericay C, et al. Efficacy of trifluridine and tipiracil (TAS-102) versus placebo, with supportive care, in a randomized, controlled trial of patients

with metastatic colorectal cancer from Spain: results of a subgroup analysis of the phase 3 RECOURSE trial. Clin Transl Oncol [Internet]. 2017 Feb [cited 2018 Jan 12];19(2):227-35. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5239803/pdf/12094_2016_Article_1528.pdf

14. Nishina T, Yoshino T, Shinozaki E, Yamazaki K, Komatsu Y, Baba H, et al. Onset of neutropenia as an indicator of treatment response in the randomized phase II of TAS-102 vs placebo in Japanese patients with metastatic colorectal cancer (Study J003- 10040030) [abstract]. J Clin Oncol [Internet]. 2016 May [cited 2018 Jan 17];34(15 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.3557

15. Mayer RJ, Van Cutsem E, Yoshino T, Falcone A, Garcia-Carbonero R, Argiles G, et al. Supportive treatment for hematologic toxicities in the phase 3 RECOURSE trial of TAS-102 vs placebo with best supportive care in patients with metastatic colorectal cancer. J Clin Oncol [Internet]. 2016 [cited 2018 Jan 17];34(15 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.e15021

16. Yoshino T, Shinozaki E, Yamazaki K, Nishina T, Komatsu Y, Baba H, et al. Final survival results and onset of neutropenia as an indicator of therapeutic effect in phase 2 of TAS-102 vs placebo with metastatic colorectal cancer (J003-10040030). Ann Oncol. 2016;107 Suppl 2:ii107.

17. Mayer RJ, Ohtsu A, Yoshino T, Falcone A, Garcia-Carbonero R, Argiles G, et al. Efficacy and safety results in patients with impaired renal and hepatic function in the RECOURSE trial [abstract]. J Clin Oncol [Internet]. 2016 [cited 2018 Jan 16];34(15 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.3547

18. Ohtsu A, Yoshino T, Wahba MM, Benedetti FM, Falcone A, Garcia-Carbonero R, et al. Phase III RECOURSE trial of TAS-102 versus placebo with best supportive care in patients with metastatic colorectal cancer: Geographic subgroups [abstract]. J Clin Oncol [Internet]. 2016 Feb [cited 2018 Jan 17];34(4 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/jco.2016.34.4_suppl.646

19. Ohtsu A, Yoshino T, Falcone A, Garcia-Carbonero R, Argiles G, Sobrero AF, et al. Onset of neutropenia as an indicator of treatment response in the phase 3 RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo in patients with metastatic colorectal cancer [abstract]. J Clin Oncol [Internet]. 2017 [cited 2018 Jan 17];35(4 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.775

20. Shinozaki E, Laurent S, Gravalos C, Benavides M, Longo MF, Mizuguchi H, et al. Timing of adverse events (AEs) in the Phase 3 RECOURSE trial of TAS-102 versus placebo in patients (pts) with metastatic colorectal cancer (mCRC). Eur J Cancer. 2015 Sep;51(Supplement 3):S383-S384.

21. Tabernero J, Mayer RJ, Ohtsu A, Yoshino T, Garcia-Carbonero R, Pastorino A, et al. RECOURSE trial: impact of adverse events on quality of life and duration of TAS-102 (trifluridine and tipiracil) treatment. Ann Oncol. 2016 Jun 1;27(Suppl. 2):ii111.

22. Van Cutsem E, Ohtsu A, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Phase III recourse trial of TAS-102 vs. placebo, with best supportive care (bsc), in patients (pts) with metastatic colorectal cancer (mcrc) refractory to standard therapies. Ann Oncol. 2014 [cited 2018 Jan 18];25(Supplement 5):v1-v41.

23. Van Cutsem E, Benedetti FM, Mizuguchi H, Mayer RJ, Ohtsu A. TAS-102 vs placebo (PBO) in patients (pts) >=65 years (y) with metastatic colorectal cancer (mCRC): an age-based analysis of the RECOURSE trial [abstract]. J Clin Oncol [Internet]. 2015 [cited 2018 Jan 17];33(15 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.3595

24. Van Cutsem E, Garcia-Carbonero R, Pastorino A, Zaniboni A, Falcone A, Amellal N, et al. RECOURSE trial: performance status at discontinuation in patients receiving trifluridine/tipiracil (TAS-102). Ann Oncol. 2016 Oct 1;27(Supplement 6):515P.

25. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Lonsurf (trifluridine and tipiracil). Company: Taiho Oncology, Inc Application no.: 207981 Approval date: 09/22/2015 [Internet]. Rockville (MD): FDA; 1800 Jan 1 [cited 2017 Nov 6]. (FDA drug approval package). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207981Orig1s000StatR.pdf

26. Canadian Cancer Registry (CCR) [Internet]. Ottawa (ON): Statistics Canada; 2013 Apr 2. [cited 2017 Dec 18]. Available from: http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=329031

27. Van Cutsem E, Ohtsu A, Leger C, Amellal N, Poirot C, Fougeray R, et al. Effect of number of prior lines versus prior regimens in pts receiving trifluridine/tipiracil (TAS-102) [anstract]. J Clin Oncol [Internet]. 2017 Feb [cited 2018 Jan 17];35(4 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.720

28. Pestana C, Reitemaier J, Moertel C, Judd E, Dockerty M. The natural history of carcinoma of the colon and rectum. Am J Surg. 1964;108(6):826-9.

29. Bengmark S, Hafstrom L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer. 1969 Jan;23(1):198-202.

30. Van Cutsem E, Mayer RJ, Laurent S, Winkler R, Gravalos C, Benavides M, et al. The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. Eur J Cancer. 2018;90()(pp 63-72), 2018. Date of Publication: February 2018.):63-72.

31. Yoshino T, Cleary J, Mayer R, Yoshida K, Makris L, Yamashita F, et al. Pharmacokinetic and pharmacodynamic (PK/PD) analysis results from the phase 3 RECOURSE trial of trifluridine and tipiracil (TAS-102) versus placebo (pbo) in patients (pts) with refractory metastatic colorectal cancer (mCRC). Ann Oncol. 2016;27 Suppl 2.

32. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Lonsurf (trifluridine / tipiracil) [Internet]. London (GB): European Medicines Agency; 2016 Feb 25. [cited 2018 Jan 18]. (European public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003897/WC500206248.pdf

33. Lenz HJ, Stintzing S, Loupakis F. TAS-102, a novel antitumor agent: a review of the mechanism of action. Cancer Treat Rev. 2015 Nov;41(9):777-83. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624296

34. Mota JM, Fonseca LG, Braghiroli MI, Hoff PM. Review on TAS-102 development and its use for metastatic colorectal cancer. Crit Rev Oncol Hematol. 2016 Aug;104:91-7.

35. Loree JM, Kopetz S. Recent developments in the treatment of metastatic colorectal cancer. Ther Adv Med Oncol. 2017 Aug;9(8):551-64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5524248

36. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol. 2004 Apr 1;22(7):1209-14.

37. Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. Lancet Oncol. 2007 Oct;8(10):898-911.

38. Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol. 2017 Aug 1;28(8):1713-29.

39. Lee GH, Malietzis G, Askari A, Bernardo D, Al-Hassi HO, Clark SK. Is right-sided colon cancer different to left-sided colorectal cancer? - a systematic review. Eur J Surg Oncol. 2015 Mar;41(3):300-8.

40. Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, et al. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Oct 27.

41. Iveson TJ, Hickish T, Schmitt C, Van CE. Irinotecan in second-line treatment of metastatic colorectal cancer: improved survival and cost-effect compared with infusional 5-FU. Eur J Cancer. 1999 Dec;35(13):1796-804.

42. Ward S, Kaltenthaler E, Cowan J, Brewer N. Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation. Health Technol Assess. 2003;7(32):1-93.

43. Hillner BE, Schrag D, Sargent DJ, Fuchs CS, Goldberg RM. Cost-effectiveness projections of oxaliplatin and infusional fluorouracil versus irinotecan and bolus fluorouracil in first-line therapy for metastatic colorectal carcinoma. Cancer. 2005 Nov 1;104(9):1871-84.

44. Tumeh JW, Shenoy PJ, Moore SG, Kauh J, Flowers C. A Markov model assessing the effectiveness and cost-effectiveness of FOLFOX compared with FOLFIRI for the initial treatment of metastatic colorectal cancer. Am J Clin Oncol. 2009 Feb;32(1):49-55.

45. Shiroiwa T, Fukuda T, Tsutani K. Cost-effectiveness analysis of XELOX for metastatic colorectal cancer based on the NO16966 and NO16967 trials. Br J Cancer. 2009 Jul 7;101(1):12-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713700

46. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet. 1998 Oct 31;352(9138):1413-8.

47. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. BMJ. 2000 Sep 2;321(7260):531-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC27466

48. Yoshino T, Uetake H, Fujita N, Furuta T, Katori J, Hara N, et al. TAS-102 Safety in Metastatic Colorectal Cancer: Results From the First Postmarketing Surveillance Study. Clin Colorectal Cancer. 2016 Dec;15(4):e205-e211.

49. McLean J, Rho YS, Kuruba G, Mamo A, Gilabert M, Kavan T, et al. Clinical Practice Patterns in Chemotherapeutic Treatment Regimens for Metastatic Colorectal Cancer. Clin Colorectal Cancer. 2016 Jun;15(2):135-40.

50. Zaniboni A, Bertocchi P, Barni S, Petrelli F. TAS-102 (Lonsurf) for the Treatment of Metastatic Colorectal Cancer. A Concise Review. Clin Colorectal Cancer. 2016 Dec;15(4):292-7.

51. Bullement A, Underhill S, Fougeray R, Hatswell AJ. Cost-effectiveness of Trifluridine/tipiracil for Previously Treated Metastatic Colorectal Cancer in England and Wales. Clin Colorectal Cancer. 2017 Sep 28.

52. Kimura M, Usami E, Iwai M, Go M, Teramachi H, Yoshimura T. Comparison of cost-effectiveness of regorafenib and trifluridine/tipiracil combination tablet for treating advanced and recurrent colorectal cancer. Mol Clin Oncol. 2016 Nov;5(5):635-40. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5103889

53. Masuishi T, Taniguchi H, Hamauchi S, Komori A, Kito Y, Narita Y, et al. Regorafenib Versus Trifluridine/Tipiracil for Refractory Metastatic Colorectal Cancer: A Retrospective Comparison. Clin Colorectal Cancer. 2017 Jun;16(2):e15-e22.

54. Suenaga M, Schirripa M, Cao S, Zhang W, Yang D, Dadduzio V, et al. Potential role of polymorphisms in the transporter genes ENT1 and MATE1/OCT2 in predicting TAS-102 efficacy and toxicity in patients with refractory metastatic colorectal cancer. Eur J Cancer. 2017 Nov;86:197-206.

55. Lee JJ, Chu E. Adherence, dosing, and managing toxicities with Trifluridine/Tipiracil (TAS-102). Clin Colorectal Cancer. 2017 Jun;16(2):85-92.

56. Abrahao ABK, Ko YJ, Berry S, Chan KKW. A Comparison of Regorafenib and TAS-102 for Metastatic Colorectal Cancer: A Systematic Review and Network Meta-analysis. Clin Colorectal Cancer. 2017 Nov 21.

57. Drug Improves Survival in Refractory Colorectal Cancer. Cancer Discov. 2015 Jul;5(7):OF3, 2015.

58. Abrahao ABK, Ko YJ, Chan KK, Berry SR. Efficacy and safety of regorafenib compared to TAS-102 for metastatic colorectal cancer: a systematic review and network meta-analysis. J Clin Oncol [Internet]. 2017 Feb [cited 2018 Jan 17];35(4 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.735

59. Christ MM. Metastatic colorectal carcinoma: Trifluridine/Tipiracil as a new option for the treatment of pretreated colorectal cancer patients. Arzneimitteltherapie. 2016;34(11):450-1. German.

60. Cleary JM, Rosen LS, Yoshida K, Rasco D, Shapiro GI, Sun W. A phase 1 study of the pharmacokinetics of nucleoside analog trifluridine and thymidine phosphorylase inhibitor tipiracil (components of TAS-102) vs trifluridine alone. Invest New Drugs [Internet]. 2017 [cited 2018 Jan 15];35(2):189-97. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5352756/pdf/10637_2016_Article_409.pdf

61. Cleghorn S. TAS-102 for metastatic refractory colorectal cancer. Lancet Oncol. 2015 Jul;16(7):e314.

62. Comeau JM, Labruzzo MB. From bench to bedside: promising colon cancer clinical trials. Am J Manag Care [Internet]. 2013 Jan [cited 2018 Jan 15];19(Special Issue 1):SP32-SP37. Available from: https://ajmc.s3.amazonaws.com/_media/_pdf/EBO_janfeb.pdf

63. Gensthaler BM. TAS-102: new cytostatic agent for colorectal cancer. Pharm Ztg. 2016;2016(161):23.

64. Goldberg R. Emerging phase 3 data in relapsed/refractory metastatic colorectal cancer. Clin Adv Hematol Oncol. 2016 Jan;14(1):30-3.

65. Kish T, Uppal P. Trifluridine/Tipiracil (Lonsurf) for the Treatment of Metastatic Colorectal Cancer. P t [Internet]. 2016 May [cited 2018 Jan 15];41(5):314-25. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4849340/pdf/ptj4105314.pdf

66. Kito Y, Hamauchi S, Yamazaki K, Komori A, Masuishi T, Taniguchi H, et al. TAS-102 in patients with metastatic colorectal cancer refractory to standard therapies including regorafenib. Ann Oncol. 2016 Jul 1;27(Supplement 7):vii78.

67. Kotaka M, Satake H, Okita Y, Hatachi Y, Kotake T, Hashida H, et al. Regorafenib vs TAS-102 as salvage-line treatment in patients with metastatic colorectal cancer refractory to standard chemotherapies: a multicenter retrospective comparison study. Ann Oncol. 2016 Jun 21;27(Supplement 2):ii47.

68. Marcus L, Lemery SJ, Khasar S, Wearne E, Helms WS, Yuan W, et al. FDA approval summary: TAS-102. Clin Cancer Res. 2017 Jun 15;23(12):2924-7.

69. Mende A. Lonsurf is approved for colon cancer. Pharm Ztg. 2016;161(18):33.

70. Ortner P. Pre-treated patients with metastatic colorectal carcinoma: Trifluridine/Tipiracil provides an opportunity for improved overall survival. Klinikarzt. 2016;45(12):640.

71. Raedler LA. Lonsurf (Trifluridine plus Tipiracil): a new oral treatment approved for patients with metastatic colorectal cancer. Am Health Drug Benefits [Internet]. 2016 Mar [cited 2018 Jan 15];9(Special Feature):97-100. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013844/pdf/ahdb-09-097.pdf

72. Sollner B. Metastatic colorectal carcinoma: lonsurf as a new therapeutic option. Journal fur Pharmakologie und Therapie. 2016;25(3):92-3. German.

73. Sugimoto N, Yoshinami T, Yamamoto S, Yagi T, Imamura F. Effect of regorafenib and TAS-102 in metastatic colorectal cancer (mCRC) patients on survival in salvage line with different toxicity profile [abstract]. J Clin Oncol [Internet]. 2016 Feb;34(Supplement 4):763. Available from: http://ascopubs.org/doi/abs/10.1200/jco.2016.34.4_suppl.763

74. Wang X, Zhou J, Li Y, Ge Y, Zhou Y, Shen L, et al. A phase I, open-label nonrandomized, pharmacokinetic study of trifluridine/tipiracil (TAS-102) in Chinese patients with solid tumors [abstract]. J Clin Oncol [Internet]. 2017 [cited 2018 Jan 17];35(15 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e14079

75. Wilhelmi E. Metastatic colorectal cancer: opportunity for a longer lifetime with trifluridine/tipiracil. Journal fur Pharmakologie und Therapie. 2016;25(5):167-9.

76. Yamaguchi K, Komatsu Y, Oki E, Yoshino T, Yamazaki K, Shibuya K, et al. APOLLON study: A phase I/II study for the safety and efficacy of panitumumab in combination with TAS-102 for patients with RAS wild-type metastatic colorectal cancer refractory to standard chemotherapy. Ann Oncol. 2016;27 Suppl 6.

77. Yoshino T. Colorectal cancer: a new oral cytotoxic agent reappears. Ann Oncol. 2012 Sep;23(Supplement 9):ix63.

78. Zoler ML. TAS-102 boosts survival with good tolerability in patients with metastatic CRC. Oncology Report [Internet]. 2014;10(10):18. Available from: http://www.oncologyreport-digital.com/oncologyreport/october_2014?pg=18#pg18

79. Trifluridine-tipiracil for previously treated metastatic colorectal cancer [Internet]. London (GB): National Institute for Health Care and Excellence (NICE); 2016 Aug 27. [cited 2018 Jan 5]. (Technology appraisal guidance [TA405]). Available from: https://www.nice.org.uk/guidance/TA405/chapter/1-Recommendations

80. Abrahao ABK, Ko YJ, Chan KK. Efficacy and safety of regorafenib compared to TAS-102 for refractory metastatic colorectal cancer. J Clin Oncol [Internet]. 2016 [cited 2018 Jan 15];34(15 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.e15010

81. Ortner P. Metastatic colorectal carcinoma: Trifluridine/tipiracil improves survival and maintains the general condition. Visceral Medicine. 2016;32(6):441.

82. Becerra CR, Yoshida K, Mizuguchi H, Patel M, Von Hoff D. A Phase 1, Open-Label, randomized, crossover study evaluating the bioavailability of TAS-102 (Trifluridine/Tipiracil) tablets relative to an oral solution containing equivalent amounts of Trifluridine and Tipiracil. J Clin Pharmacol. 2017 Jun;57(6):751-9.

83. Cleary JM, Mayer RJ, Van Cutsem E, Yamashita F, Yoshisue K, Ieiri I, et al. Population pharmacokinetic (PK) analysis of TAS-102 in patients (pts) with metastatic colorectal cancer (mCRC): results from 3 phase 1 trials and the phase 3 RECOURSE trial. J Clin Oncol. 2015 May;33(15 Suppl):2579.

84. Karthaus M, Tabernero J, Van Cutsem E, Ohtsu A, Amellal N, Cadour S, et al. QTWIST analysis in the RECOURSE trial. Oncology research and treatment. 2017 [cited 2018 Jan 15];40(Supplement 4):166. Available from: https://www.karger.com/Article/Pdf/479566

85. Tabernero J, Van Cutsem E, Ohtsu A, Amellal N, Cadour S, Fougeray R, et al. QTWIST analysis in the RECOURSE trial [abstract]. J Clin Oncol [Internet]. 2017 Feb [cited 2018 Jan 17];35(4 Suppl). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.698

86. Yamazaki K, Yoshino T, Shinozaki E, Komatsu Y, Tsuji Y, Nishina T, et al. Clinical significance of thymidine kinase 1 expression on TAS-102 treatment in RECOURSE phase III trial of TAS-102 versus placebo for metastatic colorectal cancer. Ann Oncol. Conference: 41st european society for medical oncology congress, ESMO. 2016. Denmark. Conference start: 20161007. Conference end: 20161011 27(no pagination):2016.

87. Yoshino T, Shinozaki E, Yamazaki K, Komatsu Y, Nishina T, Baba H, et al. Effect of thymidine kinase 1 expression on prognosis and treatment outcomes in refractory metastatic colorectal cancer: Results from two randomized studies of TAS- 102 versus a placebo. J Clin Oncol [Internet]. 2017 [cited 2018 Jan 15];35(4 Supplement). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.529

88. Ilson DH, Tabernero J, Shitara K, Winkler R, Nasermoaddeli A, Ding C, et al. TAGS, a randomized, double-blind, phase 3 study evaluating TAS-102 plus best supportive care vs placebo plus best supportive care in patients with metastatic gastric cancer refractory to standard treatments. J Clin Oncol [Internet]. 2016 May [cited 2018 Jan 17];34 Supplement 15. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.TPS4141

89. Scagliotti G, Nishio M, Satouchi M, Valmadre G, Niho S, Galetta D, et al. A phase 2 randomized study of TAS-102 versus topotecan or amrubicin in patients requiring second-line chemotherapy for small cell lung cancer refractory or sensitive to frontline platinum-based chemotherapy. Lung Cancer. 2016 Oct;100:20-3.

90. Sun W, Rosen LS, Rasco DW, Yoshida K, Seraj J, Shapiro G, et al. An open-label, randomized, parallel-group study of the pharmacokinetics of trifluridine as a component of TAS-102 versus FTD alone. J Clin Oncol [Internet]. 2016 Feb [cited 2018 Jan 17];34(Suppl 4). Available from: http://ascopubs.org/doi/abs/10.1200/jco.2016.34.4_suppl.751

91. Karthaus M, Van Cutsem E, Mayer RJ, Ohtsu A. TAS-102 versus placebo plus best supportive care in patients with metastatic colorectal cancer refractory to standard therapies: final survival results of the phase III RECOURSE trial. Oncology research and treatment [Internet]. 2016 Oct [cited 2018 Jan 15];39(Supplement 3):197-8. Available from: https://www.karger.com/Article/Pdf/449050

92. Kim TW, Shen L, Xu JM, Sriuranpong V, Pan H, Xu R, et al. TERRA: A randomized, double-blind, placebo-controlled phase 3 study of TAS-102 in Asian patients with metastatic colorectal cancer. Ann Oncol. 2016;27 Suppl 6.

93. Van Cutsem E, Benedetti FM, Mizuguchi H, Mayer RJ, Falcone A, Garcia-Carbonero R, et al. TAS-102 versus placebo (PBO) in patients (pts) : 65 years (y) with metastatic colorectal cancer (mCRC): An age-based analysis of the recourse trial [abstract]. J Clin Oncol [Internet]. 2016 [cited 2018 Jan 16];34(4 Suppl 1). Available from: http://ascopubs.org/doi/abs/10.1200/jco.2016.34.4_suppl.638

94. Yamazaki K, Yoshino T, Mizunuma N, Nishina T, Komatsu Y, Baba H, et al. A multicenter, randomized, double-blind, phase II study of TAS-102 plus best supportive care (BSC) (a) versus placebo plus BSC (p) in patients (pts) with chemotherapy-refractory metastatic colorectal cancer (MCRC) [abstract]. Ann Oncol. 2011;22 Suppl 9:ix1.

95. Van Cutsem E, Ohtsu A, Busto NL, Kanehisa A, Fougeray R, Winkler R, et al. Time to grade >=3 adverse events in pts receiving trifluridine/tipiracil (TAS-102) [abstract]. J Clin Oncol [Internet]. 2017 [cited 2018 Jan 16];35(4 Supplement). Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.788

96. Ohtsu A, Yoshino T, Wahba MM, Benedetti FM, Mayer RJ, Van CE. Phase 3 RECOURSE trial of TAS-102 versus placebo with best supportive care in patients with metastatic colorectal cancer: Geographic subgroups [abstract]. J Clin Oncol [Internet]. 2015 [cited 2018 Jan 16];33(15 Suppl 1). Available from: http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.3564

97. Scottish Intercollegiate Guidelines Network, Healthcare Improvement Scotland. Critical appraisal notes and checklists [Internet]. Edinburgh (GB): SIGN; 2018. [cited 2018 Jan 18]. Available from: http://www.sign.ac.uk/checklists-and-notes.html

98. Van CE, Falcone A, Garcia-Carbonero R, Komatsu Y, Pastorino A, Peeters M, et al. Proxies of quality of life in metastatic colorectal cancer: analyses in the RECOURSE trial. ESMO Open. 2017;2(5):e000261. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5708320